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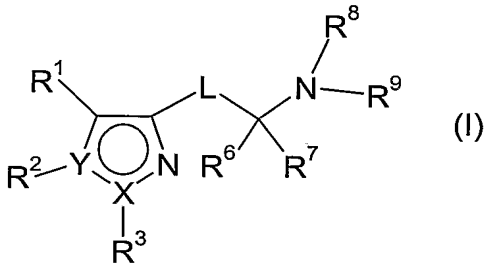
(54) Title: PYRAZOLE AND IMIDAZOLE COMPOUNDS AND USES THEREOF



(I)

(57) Abstract: Compounds of Formula (I) that act as cannabinoid receptor ligands and their uses in the treatment diseases, conditions and/or disorders modulated by cannabinoid receptor antagonists in animals are described herein.

PYRAZOLE AND IMIDAZOLE COMPOUNDS AND USES THEREOF

FIELD OF THE INVENTION

The present invention relates to pyrazole and imidazole compounds, which are useful as cannabinoid receptor ligands, in particular as CB-1 receptor antagonists. As a result, the present invention also relates to the use of the compounds in treating diseases, conditions and disorders modulated by cannabinoid receptor ligands including pharmaceutical compositions for such use.

BACKGROUND

Obesity is a major public health concern because of its increasing prevalence and associated health risks. Obesity and overweight are generally defined by body mass index (BMI), which is correlated with total body fat and estimates the relative risk of disease. BMI is calculated by weight in kilograms divided by height in meters squared (kg/m^2). Overweight is typically defined as a BMI of 25-29.9 kg/m^2, and obesity is typically defined as a BMI of 30 kg/m^2. See, e.g., National Heart, Lung, and Blood Institute, Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults, The Evidence Report, Washington, DC: U.S. Department of Health and Human Services, NIH publication no. 98-4083 (1998).

The increase in obesity is of concern because of the excessive health risks associated with obesity, including coronary heart disease, strokes, hypertension, type 2 diabetes mellitus, dyslipidemia, sleep apnea, osteoarthritis, gall bladder disease, depression, and certain forms of cancer (e.g., endometrial, breast, prostate, and colon). The negative health consequences of obesity make it the second leading cause of preventable death in the United States and impart a significant economic and

psychosocial effect on society. See, McGinnis M, Foege WH., "Actual Causes of Death in the United States," JAMA, **270**, 2207-12 (1993).

Obesity is now recognized as a chronic disease that requires treatment to reduce its associated health risks. Although weight loss is an important treatment outcome, one of the main goals of obesity management is to improve cardiovascular and metabolic values to reduce obesity-related morbidity and mortality. It has been shown that 5-10% loss of body weight can substantially improve metabolic values, such as blood glucose, blood pressure, and lipid concentrations. Hence, it is believed that a 5-10% intentional reduction in body weight may reduce morbidity and mortality.

Currently available prescription drugs for managing obesity generally reduce weight by inducing satiety or decreasing dietary fat absorption. Satiety is achieved by increasing synaptic levels of norepinephrine, serotonin, or both. For example, stimulation of serotonin receptor subtypes 1B, 1D, and 2C and 1- and 2-adrenergic receptors decreases food intake by regulating satiety. See, Bray GA, "The New Era of Drug Treatment. Pharmacologic Treatment of Obesity: Symposium Overview," Obes Res., **3**(suppl 4), 415s-7s (1995). Adrenergic agents (e.g., diethylpropion, benzphetamine, phendimetrazine, mazindol, and phentermine) act by modulating central norepinephrine and dopamine receptors through the promotion of catecholamine release. Older adrenergic weight-loss drugs (e.g., amphetamine, methamphetamine, and phenmetrazine), which strongly engage in dopamine pathways, are no longer recommended because of the risk of their abuse. Fenfluramine and dexfenfluramine, both serotonergic agents used to regulate appetite, are no longer available for use.

More recently, CB1 cannabinoid receptor antagonists/inverse agonists have been suggested as potential appetite suppressants. See, e.g., Arnone, M., *et al.*, "Selective Inhibition of Sucrose and Ethanol Intake by SR141716, an Antagonist of Central Cannabinoid (CB1) Receptors," Psychopharmacol, **132**, 104-106 (1997); Colombo, G., *et al.*, "Appetite Suppression and Weight Loss after the Cannabinoid Antagonist SR141716,"

Life Sci., **63**, PL113-PL117 (1998); Simiand, J., *et al.*, "SR141716, a CB1 Cannabinoid Receptor Antagonist, Selectively Reduces Sweet Food Intake in Marmose," Behav. Pharmacol., **9**, 179-181 (1998); and Chaperon, F., *et al.*, "Involvement of Central Cannabinoid (CB1) Receptors in the Establishment of Place Conditioning in Rats," Psychopharmacology, **135**, 324-332 (1998). For a review of cannabinoid CB1 and CB2 receptor modulators, see Pertwee, R.G., "Cannabinoid Receptor Ligands: Clinical and Neuropharmacological Considerations, Relevant to Future Drug Discovery and Development," Exp. Opin. Invest. Drugs, **9**(7), 1553-1571 (2000).

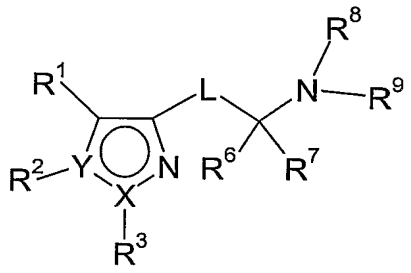
Although investigations are on-going, there still exists a need for a more effective and safe therapeutic treatment for reducing or preventing weight-gain.

In addition to obesity, there also exists an unmet need for treatment of alcohol abuse. Alcoholism affects approximately 10.9 million men and 4.4 million women in the United States. Approximately 100,000 deaths per year have been attributed to alcohol abuse or dependence. Health risks associated with alcoholism include impaired motor control and decision making, cancer, liver disease, birth defects, heart disease, drug/drug interactions, pancreatitis and interpersonal problems. Studies have suggested that endogenous cannabinoid tone plays a critical role in the control of ethanol intake. The endogenous CB1 receptor antagonist SR-141716A has been shown to block voluntary ethanol intake in rats and mice. See, Arnone, M., *et al.*, "Selective Inhibition of Sucrose and Ethanol Intake by SR141716, an Antagonist of Central Cannabinoid (CB1) Receptors," Psychopharmacol, **132**, 104-106 (1997). For a review, see Hungund, B.L and B.S. Basavarajappa, "Are Anadamide and Cannabinoid Receptors involved in Ethanol Tolerance? A Review of the Evidence," Alcohol & Alcoholism. **35**(2) 126-133, 2000.

Current treatments for alcohol abuse or dependence generally suffer from non-compliance or potential hepatotoxicity; therefore, there is a high unmet need for more effective treatment of alcohol abuse/dependence.

SUMMARY

The present invention provides compounds of Formula (I) that act as cannabinoid receptor ligands (preferably, CB1 receptor antagonists or inverse agonists).



(I)

wherein

X is carbon and Y is nitrogen or X is nitrogen and Y is carbon;

R^1 is hydrogen, $(C_1\text{-}C_6)$alkyl, halogen, or cyano;

R^2 and R^3 are each independently $(CH_2)_n$-aryl or $(CH_2)_n$-heteroaryl, where n is 0, 1 or 2, and where the aryl and the heteroaryl moieties are optionally substituted with one or more substituents (see list of substituents in the definition section below);

L is -C(O)- or $-C(R^4)(OR^5)-$, where R^4 is hydrogen or $(C_1\text{-}C_6)$alkyl and R^5 is hydrogen, $(C_1\text{-}C_6)$alkyl, or taken together with R^8 or R^9 is $-CH_2CH_2-$ or $-CH_2C(O)-$;

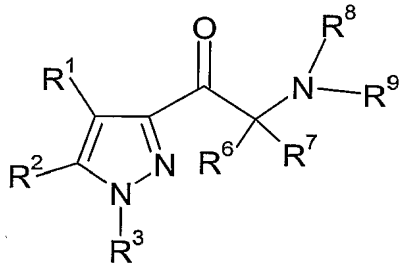
R^6 and R^7 are each independently hydrogen or $(C_1\text{-}C_6)$alkyl, or R^6 and R^7 taken together form a partially or fully saturated carbocyclic ring; and

R^8 and R^9 are each independently hydrogen, $(C_1\text{-}C_6)$alkyl, $-C(O)(CH_2)_mR^{10}$, $-SO_2(CH_2)_nR^{10}$, or $-(CH_2)_pR^{10}$, where m and n are 0, 1, or 2, p is 0, 1, 2 or 3, and R^{10} is selected from the group consisting of $(C_1\text{-}C_8)$alkyl, a partially or fully saturated cycloalkyl, aryl, heteroaryl, and a partially or fully saturated heterocycle, where the $(C_1\text{-}C_8)$alkyl, the cycloalkyl, the aryl, the heteroaryl and the heterocycle are optionally substituted with one or more substituents (see list of substituents in the definition section below); or

R^8 and R^9 taken together form a partially or fully saturated, 4- to 8-membered heterocyclic ring containing 1 to 3 heteroatoms and optionally substituted with one or more substituents (see list of substituents in the definition section below);

a pharmaceutically acceptable salt thereof, a prodrug of the compound or the salt, or a solvate or hydrate of the compound, the salt or the prodrug.

In a preferred embodiment, a compound of Formula (IA) is provided.



(IA)

wherein

R^1 is hydrogen or $(C_1\text{-}C_6)$alkyl;

R^2 and R^3 are each independently $-(CH_2)_n$-aryl or $-(CH_2)_n$-heteroaryl, where n is 0, 1 or 2, and where the aryl and the heteroaryl moieties are optionally substituted with one to three substituents (preferably, n is 0, R^2 is *p*-chlorophenyl or *p*-fluorophenyl, and R^3 is 2,4-dichlorophenyl, 2-chlorophenyl or 2-flurorophenyl);

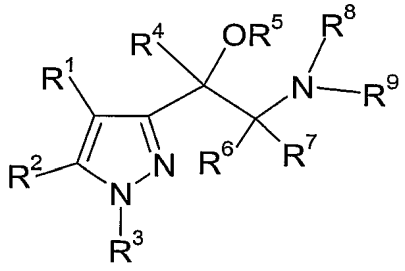
R^6 and R^7 are each independently hydrogen or $(C_1\text{-}C_6)$alkyl, or R^6 and R^7 taken together form a partially or fully saturated carbocyclic ring; and

R^8 and R^9 taken together form a partially or fully saturated, 5- to 7-membered heterocyclic ring containing 1 to 3 heteroatoms and optionally substituted with one or more substituents (see list of substituents in the definition section below);

a pharmaceutically acceptable salt thereof, a prodrug of the compound or the salt, or a solvate or hydrate of the compound, the salt or the prodrug.

Preferred compounds of Formula IA include: 1-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-piperidin-1-yl-ethanone; 1-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-morpholin-4-yl-ethanone; 1-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-(1-methyl-1H-pyrrole-2-carbonyl)-piperazin-1-yl]-ethanone; 1-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-(1-methyl-cyclopropanecarbonyl)-piperazin-1-yl]-ethanone; N-(1-{2-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-piperidin-4-yl)-2,2,2-trifluoro-acetamide; 1-[5-(4-chloro-phenyl)-1-(2-fluoro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-morpholin-4-yl-ethanone; 1-[5-(4-chloro-phenyl)-1-(2-fluoro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-piperidin-1-yl-ethanone; 1-[5-(4-chloro-phenyl)-1-(2-fluoro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-(4-trifluoroacetyl-piperazin-1-yl)-ethanone; 1-[1-(2-chloro-phenyl)-5-(4-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-pyrrolidin-1-yl-ethanone; 1-[1-(2-chloro-phenyl)-5-(4-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-[1,4]oxazepan-4-yl-ethanone; and 1-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-(1-oxa-8-aza-spiro[4.5]dec-8-yl)-ethanone; a pharmaceutically acceptable salt thereof, a prodrug of the compound or the salt, or a solvate or hydrate of the compound, the salt or the prodrug

In another preferred embodiment of the present invention, compounds of Formula (IB) are provided.



(IB)

wherein

R^1 is hydrogen or $(C_1\text{-}C_6)$alkyl;

R^2 and R^3 are each independently -$(CH_2)_n$-aryl or -$(CH_2)_n$-heteroaryl, where n is 0, 1 or 2, and where the aryl and the heteroaryl moieties are optionally substituted with one to three substituents (preferably, n is 0, R^2 is *p*-chlorophenyl or *p*-fluorophenyl, and R^3 is 2,4-dichlorophenyl, 2-chlorophenyl or 2-flurorophenyl);

R^4 is hydrogen or (C_1-C_6)alkyl;

R^5 is hydrogen or (C_1-C_6)alkyl;

R^6 and R^7 are each independently hydrogen or (C_1-C_6)alkyl, or R^6 and R^7 taken together form a partially or fully saturated carbocyclic ring; and

R^8 and R^9 are each independently hydrogen, (C_1-C_6)alkyl, -$C(O)(CH_2)_mR^{10}$, -$SO_2(CH_2)_nR^{10}$, or -$(CH_2)_pR^{10}$, where m and n are 0, 1, or 2, p is 0, 1, 2 or 3, and R^{10} is selected from the group consisting of a (C_1-C_8)alkyl, a partially or fully saturated cycloalkyl, aryl, heteroaryl, and a partially or fully saturated heterocycle, where the (C_1-C_8)alkyl, the cycloalkyl, the aryl, the heteroaryl and the heterocycle are optionally substituted with one or more substituents (see list of substituents in the definition section below), or

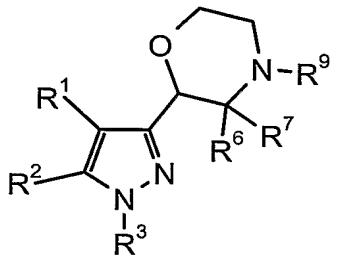
R^8 and R^9 taken together form a partially or fully saturated, 5- to 7-membered heterocyclic ring containing 1 to 3 heteroatoms and optionally substituted with one or more substituents (see list of substituents in the definition section below);

a pharmaceutically acceptable salt thereof, a prodrug of the compound or the salt, or a solvate or hydrate of the compound, the salt or the prodrug.

Preferred compounds of Formula IB include: 2-(benzyl-isopropyl-amino)-1-[1-(2-chloro-phenyl)-5-(4-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-ethanol; 1-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-(3,5-dimethyl-piperidin-1-yl)-ethanol; 1-{2-[1-(2-chloro-phenyl)-5-(4-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-hydroxy-ethyl}-4-isopropylamino-piperidine-4-carboxylic acid amide; 1-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-(3,3-dimethyl-piperidin-1-yl)-ethanol; 1-

[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-piperidin-1-yl-ethanol; and 1-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-morpholin-4-yl-ethanol; a pharmaceutically acceptable salt thereof, a prodrug of the compound or the salt, or a solvate or hydrate of the compound, the salt or the prodrug.

In yet another preferred embodiment of the present invention, compounds of Formula (IC) are provided.



(IC)

wherein

R^1 is hydrogen or $(C_1\text{-}C_6)$alkyl;

R^2 and R^3 are each independently $-(CH_2)_n$-aryl or $-(CH_2)_n$-heteroaryl, where n is 0, 1 or 2, and where the aryl and the heteroaryl moieties are optionally substituted with one to three substituents (preferably, n is 0, R^2 is *p*-chlorophenyl or *p*-fluorophenyl, and R^3 is 2,4-dichlorophenyl, 2-chlorophenyl or 2-flurorophenyl);

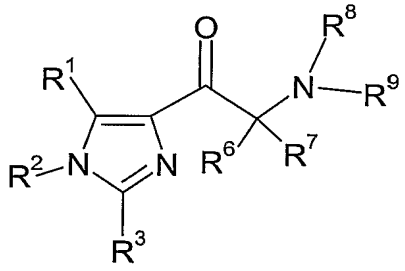
R^6 and R^7 are each independently hydrogen or $(C_1\text{-}C_6)$alkyl, or R^6 and R^7 taken together form a partially or fully saturated carbocyclic ring; and

R^9 is hydrogen, $(C_1\text{-}C_6)$alkyl, $-C(O)(CH_2)_mR^{10}$, $-SO_2(CH_2)_nR^{10}$, or $-(CH_2)_pR^{10}$, where m and n are 0, 1, or 2, p is 0, 1, 2 or 3, and R^{10} is selected from the group consisting of $(C_1\text{-}C_8)$alkyl, a partially or fully saturated cycloalkyl, aryl, heteroaryl, and a partially or fully saturated heterocycle, where the $(C_1\text{-}C_8)$alkyl, the cycloalkyl, the aryl, the heteroaryl and the heterocycle are optionally substituted with one or more substituents (see list of substituents in the definition section below);

a pharmaceutically acceptable salt thereof, a prodrug of the compound or the salt, or a solvate or hydrate of the compound, the salt or the prodrug.

Preferred compounds of Formula (IC) include: 2-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-4-cyclohexyl-morpholine; 2-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-4-(propane-2-sulfonyl)-morpholine; 2-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-4-(toluene-4-sulfonyl)-morpholine; 1-{2-[1-(2-chloro-phenyl)-5-(4-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-morpholin-4-yl}-2-methyl-propan-1-one; and 2-[1-(2-chloro-phenyl)-5-(4-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-4-(4-trifluoromethyl-benzyl)-morpholine; a pharmaceutically acceptable salt thereof or a solvate or hydrate of the compound or the salt.

In yet another embodiment of the present invention, a compound of Formula (ID) is provided.



(ID)

wherein

R^1 is hydrogen or $(C_1\text{-}C_6)$alkyl;

R^2 and R^3 are each independently $-(CH_2)_n$-aryl or $-(CH_2)_n$-heteroaryl, where n is 0, 1 or 2, and where the aryl and the heteroaryl moieties are optionally substituted with one to three substituents (preferably, n is 0, R^2 is *p*-chlorophenyl or *p*-fluorophenyl, and R^3 is 2,4-dichlorophenyl, 2-chlorophenyl or 2-fluorophenyl);

R^6 and R^7 are each independently hydrogen or $(C_1\text{-}C_6)$alkyl, or R^6 and R^7 taken together form a partially or fully saturated carbocyclic ring; and

R^8 and R^9 taken together form a partially or fully saturated, 5- to 7-membered heterocyclic ring containing 1 to 3 heteroatoms and optionally substituted with one or more substituents (see list of substituents in the definition section below);

a pharmaceutically acceptable salt thereof, a prodrug of the compound or the salt, or a solvate or hydrate of the compound, the salt or the prodrug.

Preferred compounds of formula (ID) include: 1-[1-(4-chloro-phenyl)-2-(2,4-dichloro-phenyl)-5-methyl-1H-imidazol-4-yl]-2-piperidin-1-yl-ethanone and 1-[1-(4-chloro-phenyl)-2-(2,4-dichloro-phenyl)-5-methyl-1H-imidazol-4-yl]-2-morpholin-4-yl-ethanone; a pharmaceutically acceptable salt thereof, a or a solvate or hydrate of the compound, or the salt.

Some of the compounds described herein contain at least one chiral center; consequently, those skilled in the art will appreciate that all stereoisomers (e.g., enantiomers and diastereoisomers) of the compounds illustrated and discussed herein are within the scope of the present invention. In addition, tautomeric forms of the compounds are also within the scope of the present invention.

In another aspect of the present invention, a pharmaceutical composition is provided that comprises (1) a compound of the present invention, and (2) a pharmaceutically acceptable excipient, diluent, or carrier.

In yet another embodiment of the present invention, a method for treating a disease, condition or disorder modulated by a cannabinoid receptor (preferably, a CB1 receptor) antagonists in animals that includes the step of administering to an animal in need of such treatment a therapeutically effective amount of a compound of the present invention (or a pharmaceutical composition thereof). Diseases, conditions, and/or disorders modulated by cannabinoid receptor antagonists include weight loss (e.g., reduction in calorie or food intake, and/or appetite suppression), obesity, bulimia, depression, atypical depression, bipolar disorders, psychoses, schizophrenia, behavioral addictions (e.g., gambling), suppression of

reward-related behaviors (e.g., conditioned place avoidance, such as suppression of cocaine- and morphine-induced conditioned place preference), alcoholism (e.g., alcohol abuse, addiction and/or dependence including abstinence, craving reduction and relapse prevention of alcohol intake), tobacco abuse (e.g., smoking addiction, cessation and/or dependence including craving reduction and relapse prevention of tobacco smoking), memory loss, Alzheimer's disease, dementia of aging, seizure disorders, epilepsy, gastrointestinal disorders (e.g., dysfunction of gastrointestinal motility or intestinal propulsion), and type II diabetes. In a preferred embodiment, the method is used in the treatment of obesity, alcoholism and/or tobacco abuse.

Compounds of the present invention may be administered in combination with at least one additional pharmaceutical agent. Preferred agents include nicotine partial agonists, opioid antagonists (e.g., naltrexone and nalmefene), dopaminergic agents (e.g., apomorphine), and anti-obesity agents, such as apo-B/MTP inhibitors, MCR-4 agonists, CCK-A agonists, monoamine reuptake inhibitors, sympathomimetic agents, β_3 adrenergic receptor agonists, dopamine agonists, melanocyte-stimulating hormone receptor analogs, 5-HT2c receptor agonists, melanin concentrating hormone antagonists, leptin, leptin analogs, leptin receptor agonists, galanin antagonists, lipase inhibitors, bombesin agonists, neuropeptide-Y antagonists, thyromimetic agents, dehydroepiandrosterone or analogs thereof, glucocorticoid receptor antagonists, orexin receptor antagonists, glucagon-like peptide-1 receptor agonists, ciliary neurotrophic factors, human agouti-related protein antagonists, ghrelin receptor antagonists, histamine 3 receptor antagonists or inverse agonists, and neuromedin U receptor agonists, and the like.

The combination therapy may be administered as (a) a single pharmaceutical composition which comprises a compound of the present invention, at least one additional pharmaceutical agent described above and a pharmaceutically acceptable excipient, diluent, or carrier; or (b) two

separate pharmaceutical compositions comprising (i) a first composition comprising a compound of the present invention and a pharmaceutically acceptable excipient, diluent, or carrier, and (ii) a second composition comprising at least one additional pharmaceutical agent described above and a pharmaceutically acceptable excipient, diluent, or carrier. The pharmaceutical compositions may be administered simultaneously or sequentially and in any order.

In yet another aspect of the present invention, a pharmaceutical kit is provided for use by a consumer to treat diseases, conditions and/or disorders modulated by cannabinoid receptor antagonists in an animal. The kit comprises a) a suitable dosage form comprising a compound of the present invention; and b) instructions describing a method of using the dosage form to treat diseases linked to the modulation of the cannabinoid receptor (preferably, the CB1 receptor).

In yet another embodiment of the present invention is a pharmaceutical kit comprising: a) a first dosage form comprising (i) a compound of the present invention and (ii) a pharmaceutically acceptable carrier, excipient or diluent; b) a second dosage form comprising (i) an additional pharmaceutical agent described above, and (ii) a pharmaceutically acceptable carrier, excipient or diluent; and c) a container.

Definitions

As used herein, the term "alkyl" refers to a hydrocarbon radical of the general formula C_nH_{2n+1}. The alkane radical may be straight or branched. For example, the term "(C_1-C_6)alkyl" refers to a monovalent, straight, or branched aliphatic group containing 1 to 6 carbon atoms (e.g., methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *s*-butyl, *t*-butyl, *n*-pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, neopentyl, 3,3-dimethylpropyl, hexyl, 2-methylpentyl, and the like). The alkane radical may be unsubstituted or substituted with one or more substituents (generally, one to three substituents except in the case of halogen substituents such as perchloro or perfluoroalkyls) selected from the group of substituents listed below in the

definition for "substituted." For example, "halo-substituted alkyl" refers to an alkyl group substituted with one or more halogen atoms (e.g., fluoromethyl, difluoromethyl, trifluoromethyl, perfluoroethyl, and the like). Similarly, the alkyl portion of an alkoxy, alkylamino, dialkylamino, and alkylthio group has the same definition as above.

The terms "partially or fully saturated carbocyclic ring" (also referred to as "partially or fully saturated cycloalkyl") refers to nonaromatic rings that are either partially or fully hydrogenated and may exist as a single ring, bicyclic ring or a spiro-fused ring. For example, partially or fully saturated carbocyclic rings (or cycloalkyl) include groups such as cyclopropyl, cyclopropenyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclpentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl, norbornyl (bicyclo[2.2.1]heptyl), norbornenyl, bicyclo[2.2.2]octyl, and the like. Generally, the carbocyclic ring is a 3 to 8 membered ring. In addition, the partially saturated or fully saturated cycloalkyl may be optionally substituted with one of more substituents (typically, one to three substituents) selected from the group of substituents listed below in the definition for "substituted." A substituted carbocyclic or heterocyclic ring includes groups wherein the carbocyclic ring is fused to a phenyl ring (e.g., indanyl, etc.) or a heteroaryl ring. The carbocyclic group may be attached to the chemical entity or moiety by any one of the carbon atoms within the carbocyclic ring system.

The term "partially saturated or fully saturated heterocyclic ring" (also referred to as "heterocycle") refers to nonaromatic rings that are either partially or fully hydrogenated and may exist as a single ring, bicyclic ring or a spiro-fused ring. Partially saturated or fully saturated heterocyclic rings include groups such as epoxy, aziridinyl, tetrahydrofuranyl, dihydrofuranyl, dihydropyridinyl, pyrrolidinyl, N-methylpyrrolidinyl, imidazolidinyl, imidazolinyl, piperidinyl, piperazinyl, pyrazolidinyl, 2H-pyranyl, 4H-pyranyl, 2H-chromenyl, oxazinyl, morpholino, thiomorpholino, tetrahydrothienyl, tetrahydrothienyl 1,1-dioxide, and the like. Generally, the heterocycle is 3 to 8 membered ring containing 1 to 3 heteroatoms selected from oxygen, sulfur

and nitrogen. In addition, the partially saturated or fully saturated heterocyclic groups may be optionally substituted with one of more substituents (typically, one to three substituents) selected from the group of substituents listed below in the definition for "substituted." A substituted heterocyclic ring includes groups wherein the heterocyclic ring is fused to a phenyl ring (e.g., 2,3-dihydrobenzofuranyl, 2,3-dihydroindolyl, 2,3-dihydrobenzothiophenyl, 2,3-dihydrobenzothiazolyl, etc.) or a heteroaryl ring. The heterocyclic group may be attached to the chemical entity or moiety by any one of the atoms within the heterocyclic ring system.

The term "alkenyl" refers to a hydrocarbon containing at least one carbon-carbon double bond. As described above for alkyl, the alkene radical may be straight or branched and the alkene radical may be unsubstituted or substituted with one or more substituents (typically, one to three substituents except for perhalo substitutions) selected from the group of substituents listed below in the definition for "substituted." The term "alkene" also includes all diastereoisomers (e.g., *cis* and *trans* isomers).

The term "aryl" or "aromatic carbocyclic ring" refers to aromatic moieties having single (e.g., phenyl) or fused ring system (e.g., naphthalene, anthracene, phenanthrene, etc.). Unless indicated otherwise, the aryl groups may be unsubstituted or substituted with one or more substituents (preferably no more than three substituents) selected from the group of substituents listed below in the definition for "substituted." Substituted aryl groups include a chain of aromatic moieties (e.g., biphenyl, terphenyl, phenylnaphthalyl, etc.) The aryl group may be attached to the chemical entity or moiety by any one of the carbon atoms within the aromatic ring system. Preferred aryl substituents are halogens (F, Cl, Br or I, preferably F or Cl), (C_1-C_4)alkoxy, (C_1-C_4)alkyl, halo-substituted(C_1-C_4)alkyl (e.g., CH_2F, CHF_2 and CF_3) and cyano. Similarly, the aryl portion (i.e., aromatic moiety) of an aroyl or aroyloxy (i.e., (aryl)-C(O)-O-) has the same definition as above.

The term "heteroaryl" or "heteroaromatic ring" refers to aromatic moieties containing at least one heteratom (e.g., oxygen, sulfur, nitrogen or combinations thereof) within the aromatic ring system (e.g., pyrrolyl, pyridyl, pyrazolyl, indolyl, indazolyl, thienyl, furanyl, benzofuranyl, oxazolyl, imidazolyl, tetrazolyl, triazinyl, pyrimidyl, pyrazinyl, thiazolyl, purinyl, benzimidazolyl, quinolinyl, isoquinolinyl, benzothiophenyl, benzoxazolyl, etc.). The heteroaromatic moiety may consist of a single or fused ring system. A typical single heteroaryl ring is a 5- to 6-membered ring containing one to three heteroatoms selected from oxygen, sulfur and nitrogen and a typical fused heteroaryl ring system is a 9- to 10-membered ring system containing one to four heteroatoms selected from oxygen, sulfur and nitrogen. Unless specified otherwise, the heteroaryl groups may be unsubstituted or substituted with one or more substituents (preferably no more than three substituents) selected from the group of substituents listed below in the definition for "substituted." The heteroaryl group may be attached to the chemical entity or moiety by any one of the atoms within the aromatic ring system (e.g., imidazol-1-yl, imidazol-2-yl, imidazol-4-yl, imidazol-5-yl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, pyrid-5-yl, or pyrid-6-yl). Similarly, the heteroaryl portion (i.e., heteroaromatic moiety) of a heteroaroyl (i.e., (heteroaryl)-C(O)-O-) has the same definition as above.

The term "acyl" refers to alkyl, partially saturated or fully saturated cycloalkyl, partially saturated or fully saturated heterocycle, aryl, and heteroaryl substituted carbonyl groups. For example, acyl includes groups such as (C_1-C_6)alkanoyl (e.g., formyl, acetyl, propionyl, butyryl, valeryl, caproyl, *t*-butylacetyl, etc.), (C_3-C_6)cycloalkylcarbonyl (e.g., cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl, etc.), heterocyclic carbonyl (e.g., pyrrolidinylcarbonyl, pyrrolid-2-one-5-carbonyl, piperidinylcarbonyl, piperazinylcarbonyl, tetrahydrofuranylcarbonyl, etc.), aroyl (e.g., benzoyl) and heteroaroyl (e.g., thiophenyl-2-carbonyl, thiophenyl-3-carbonyl, furanyl-2-carbonyl, furanyl-3-carbonyl, 1H-pyrroyl-2-carbonyl, 1H-pyrroyl-3-carbonyl, benzo[b]thiophenyl-

2-carbonyl, etc.). In addition, the alkyl, cycloalkyl, heterocycle, aryl and heteroaryl portion of the acyl group may be any one of the groups described in the respective definitions above. Unless indicated otherwise, the acyl group may be unsubstituted or optionally substituted with one of more substituents (typically, one to three substituents) selected from the group of substituents listed below in the definition for "substituted."

The term "substituted" specifically envisions and allows for substitutions that are common in the art. However, it is generally understood by those skilled in the art that the substituents should be selected so as to not adversely affect the pharmacological characteristics of the compound or adversely interfere with the use of the medicament. Those skilled in the art will also appreciate that some substitutions may be inherently unstable and therefore do not form a part of this invention. Suitable substituents for any of the groups defined above include (C_1-C_6)alkyl, partially or fully saturated (C_3-C_7)cycloalkyl, (C_2-C_6)alkenyl, aryl, heteroaryl, partially or fully saturated 3- to 6-membered heterocycle, halo (e.g., chloro, bromo, iodo and fluoro), cyano, hydroxy, (C_1-C_6)alkoxy, aryloxy, sulfhydryl (mercapto), (C_1-C_6)alkylthio, arylthio, amino, mono- or di-(C_1-C_6)alkyl amino, quaternary ammonium salts, amino(C_1-C_6)alkoxy, aminocarboxylate (i.e., -NH-C(O)-O-(C_1-C_6)alkyl), N-(C_1-C_6)alkylaminocarboxylate, hydroxy(C_1-C_6)alkylamino, amino(C_1-C_6)alkylthio, cyanoamino, formamido, acylamino (e.g., acetamido and benzamido), N-(C_1-C_6)alkyl-acylamino (e.g., N-methylacetamido), nitro, (C_1-C_6)carbamyl, keto (oxy), acyl, (C_1-C_6)alkoxycarbonyl, aryloxycarbonyl, (C_1-C_6)carboxy, glycolyl, glycyl, hydrazino, guanyl, sulfamyl, sulfonyl, sulfinyl, thio(C_1-C_6)carbonyl, thio(C_1-C_6)carboxy, and combinations thereof. In the case of substituted combinations, such as "substituted aryl(C_1-C_6)alkyl", either the aryl or the alkyl group may be substituted, or both the aryl and the alkyl groups may be substituted with one or more substituents (typically, one to three substituents except in the case of perhalo substitutions). An aryl substituted carbocyclic or heterocyclic group may be a fused ring (e.g.,

indanyl, dihydrobenzofuranyl, dihydroindolyl, etc.).A cycloalkyl substituted carbocyclic or heterocyclic group may be a spiro-fused ring.

The term "solvate" refers to a molecular complex of a compound of the present invention with one or more solvent molecules. Such solvent molecules are those commonly used in the pharmaceutical art, which are known to be innocuous to the recipient, e.g., water, ethanol, and the like. The term "hydrate" refers to the complex where the solvent molecule is water.

The term "protecting group" or "Pg" refers to a substituent that is commonly employed to block or protect a particular functionality while reacting other functional groups on the compound. For example, an "amino-protecting group" is a substituent attached to an amino group that blocks or protects the amino functionality in the compound. Suitable amino-protecting groups include acetyl, trifluoroacetyl, *t*-butoxycarbonyl (BOC), benzyloxycarbonyl (CBz) and 9-fluorenylmethylenoxycarbonyl (Fmoc). Similarly, a "hydroxy-protecting group" refers to a substituent of a hydroxy group that blocks or protects the hydroxy functionality. Suitable protecting groups include acetyl and silyl. A "carboxy-protecting group" refers to a substituent of the carboxy group that blocks or protects the carboxy functionality. Common carboxy-protecting groups include $-CH_2CH_2SO_2Ph$, cyanoethyl, 2-(trimethylsilyl)ethyl, 2-(trimethylsilyl)ethoxymethyl, 2-(*p*-toluenesulfonyl)ethyl, 2-(*p*-nitrophenylsulfenyl)ethyl, 2-(diphenylphosphino)-ethyl, nitroethyl and the like. For a general description of protecting groups and their use, see T. W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York, 1991.

The phrase "therapeutically effective amount" means an amount of a compound of the present invention that (i) treats or prevents the particular disease, condition, or disorder, (ii) attenuates, ameliorates, or eliminates one or more symptoms of the particular disease, condition, or disorder, or (iii) prevents or delays the onset of one or more symptoms of the particular disease, condition, or disorder described herein.

The term "animal" refers to humans (male and female), companion animals (e.g., dogs, cats and horses), food-source animals, zoo animals, marine animals, birds and other similar animal species. "Edible animals" refers to food-source animals such as cows, pigs, sheep and poultry.

The phrase "pharmaceutically acceptable" indicates that the substance or composition must be compatible chemically and/or toxicologically, with the other ingredients comprising a formulation, and/or the mammal being treated therewith.

The phrase "modulated by a cannabinoid receptor" or "modulation of a cannabinoid receptor" refers to the activation or deactivation of cannabinoid receptors. For example, the ligand (i.e., compound of the present invention) may act as an agonist, partial agonist, inverse agonist, antagonist, partial antagonist, and the like.

The term "antagonist" refers to both full and partial antagonists as well as inverse agonists.

The terms "treating", "treat", or "treatment" embrace both preventative, i.e., prophylactic, and palliative treatment.

The term "compounds of the present invention" (unless specifically identified otherwise) refer to compounds of Formula (I), (IA), (IB), (IC), (ID) prodrugs thereof, pharmaceutically acceptable salts of the compounds, and/or prodrugs, and hydrates or solvates of the compounds, salts, and/or prodrugs, as well as, all stereoisomers (including diastereoisomers and enantiomers), tautomers and isotopically labeled compounds.

DETAILED DESCRIPTION

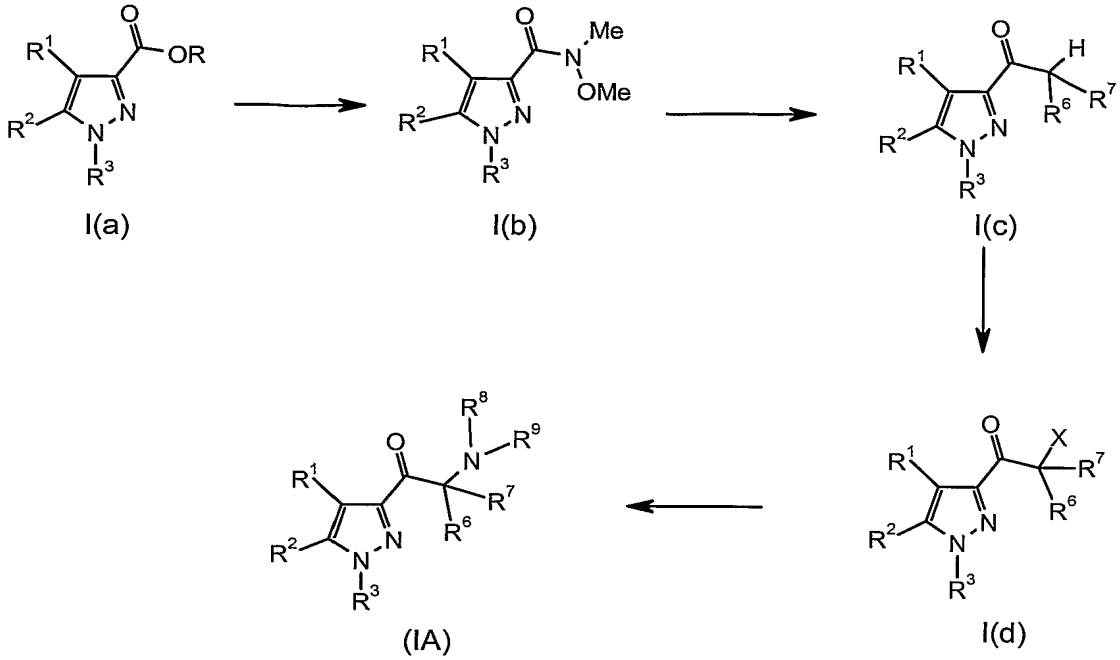
Compounds of the present invention may be synthesized by synthetic routes that include processes analogous to those well-known in the chemical arts, particularly in light of the description contained herein. The starting materials are generally available from commercial sources such as Aldrich Chemicals (Milwaukee, WI) or are readily prepared using methods well known to those skilled in the art (e.g., prepared by methods generally

described in Louis F. Fieser and Mary Fieser, Reagents for Organic Synthesis, v. 1-19, Wiley, New York (1967-1999 ed.), or Beilsteins Handbuch der organischen Chemie, 4, Aufl. ed. Springer-Verlag, Berlin, including supplements (also available *via* the Beilstein online database)).

For illustrative purposes, the reaction schemes depicted below provide potential routes for synthesizing the compounds of the present invention as well as key intermediates. For a more detailed description of the individual reaction steps, see the Examples section below. Those skilled in the art will appreciate that other synthetic routes may be used to synthesize the inventive compounds. Although specific starting materials and reagents are depicted in the schemes and discussed below, other starting materials and reagents can be easily substituted to provide a variety of derivatives and/or reaction conditions. In addition, many of the compounds prepared by the methods described below can be further modified in light of this disclosure using conventional chemistry well known to those skilled in the art.

In the preparation of compounds of the present invention, protection of remote functionality (e.g., primary or secondary amine) of intermediates may be necessary. The need for such protection will vary depending on the nature of the remote functionality and the conditions of the preparation methods. Suitable amino-protecting groups (NH-Pg) include acetyl, trifluoroacetyl, *t*-butoxycarbonyl (BOC), benzyloxycarbonyl (CBz) and 9-fluorenylmethyleneoxycarbonyl (Fmoc). The need for such protection is readily determined by one skilled in the art. For a general description of protecting groups and their use, see T. W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York, 1991.

Scheme I illustrates an efficient method for preparing compounds of Formula (I) where L is a carbonyl group or compounds of Formula (IA).

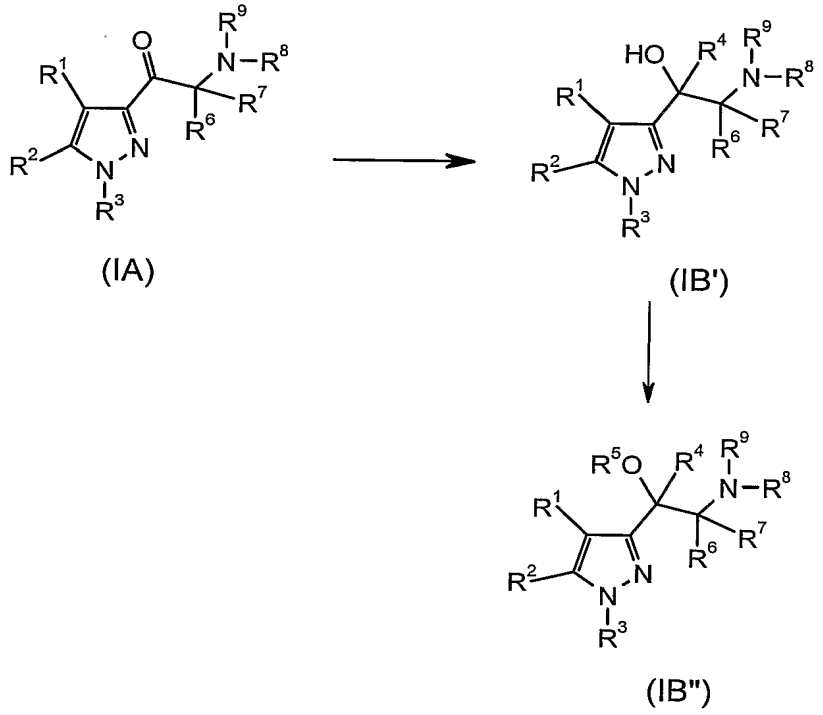


Scheme I

Ester I(a) where R^2 and R^3 are aryl groups may be prepared using analogous procedures described in U.S. Patent Nos. 4,944,790, 5,051,518, 5,134,142, and 5,624,941, all of which are incorporated herein by reference, or esterification of the corresponding carboxylic acid prepared by analogous procedures described in Bischler, Chemische Berichte, **26**, 1881-1890 (1893). Other 1,5-disubstituted aryl and heteroaryl pyrazole ester derivatives may be prepared using analogous procedures.

The amide I(b) is then prepared from the ester I(a) by reacting the ester with N,O-dimethylhydroxylamine hydrochloride and isopropylmagnesium chloride in an aprotic solvent (e.g.,THF). The N-methoxyamide I(b) is converted to the ketone I(c) by reacting with R^6R^7CH-metal (preferably, magnesium or lithium). The α-haloketone I(d) is prepared using standard halogenation procedures well known to those skilled in the art (e.g., $CuBr_2$ in refluxing ethyl acetate/chloroform). The α-halo group is then displaced with the desired amino group to provide the α-aminoketo compound IA. For example, α-halo intermediate I(d) is reacted with R^8R^9NH

in the presence of an organic or inorganic base and an aprotic solvent (e.g., diethylisopropylamine and DMSO).



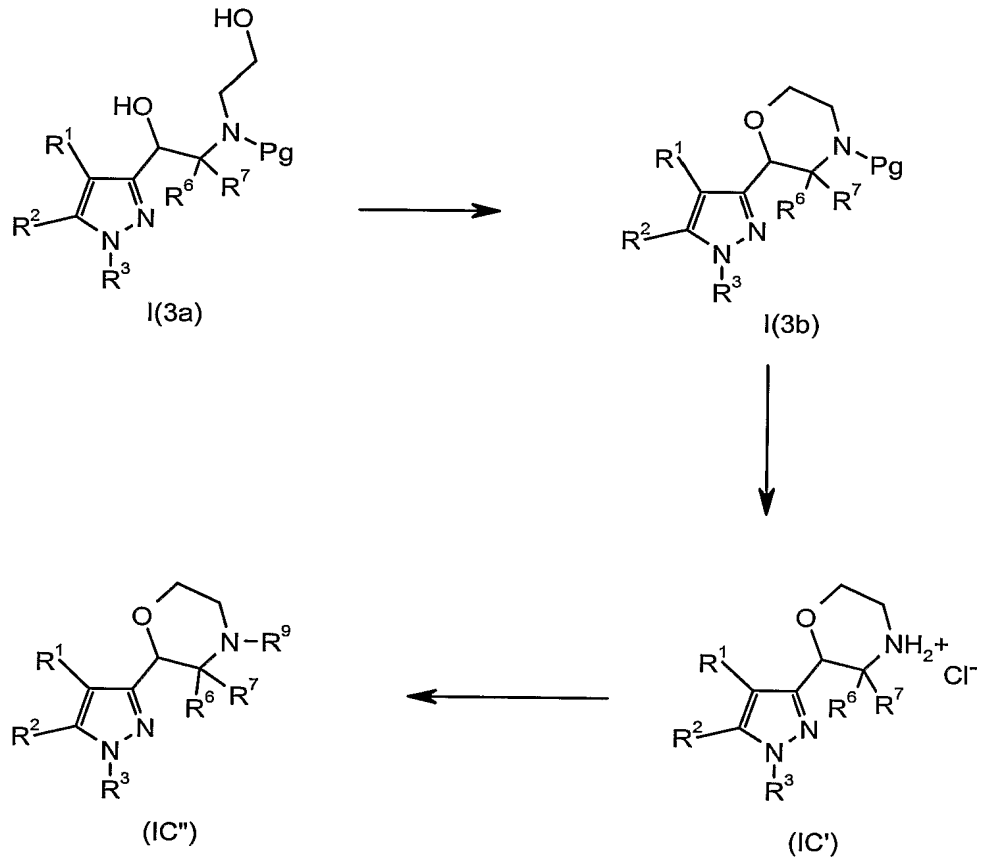
(IA) (IB') (IB")

Scheme II

As illustrated in Scheme II above, the compound of Formula (I) where L is a carbonyl group can be converted to a compound of Formula (I) where L is a hydroxymethylene (or a compound of Formula (IB) where R^4 and R^5 are both hydrogen) by reducing the carbonyl group to its corresponding alcohol. Procedures for reducing ketones to their corresponding alcohols are well-known to those skilled in the art. One convenient method is reduction with sodium borohydride in a protic solvent (e.g., ethanol) to produce a compound of Formula (I) where L is -CH(OH)-. Alternatively, compound IA can be reduced with an organometallic reagent (e.g., lithium or magnesium organometallic, such as R^4Li or R^4MgBr, dissolved in a nonreactive solvent, typically dry ethyl ether) to produce Compound (IB') (i.e., a compound of Formula (I) where L is $-CR^4(OH)-$ or a compound of Formula (IB) where R^5 is hydrogen and R^4 is (C_1-C_6)alkyl).

Compound IB' can be easily converted to its corresponding ether IB" (i.e., compounds of Formula (I) where L is $-CR^4(OR^5)-$ or compounds of Formula (IB) where R^4 is hydrogen or (C_1-C_6)alkyl and R^5 is (C_1-C_6)alkyl) using standard etherization processes well-known to those skilled in the art. For example, treatment of the alcohol IB' with an alkyl halide (e.g., R^5X) in the presence of a strong base (e.g., sodium hydride) in an aprotic solvent (e.g., dimethylformamide).

Scheme III below illustrates the preparation of compounds of the present invention where R^5 is taken together with either R^8 or R^9 to form a $-CH_2CH_2-$ linkage.

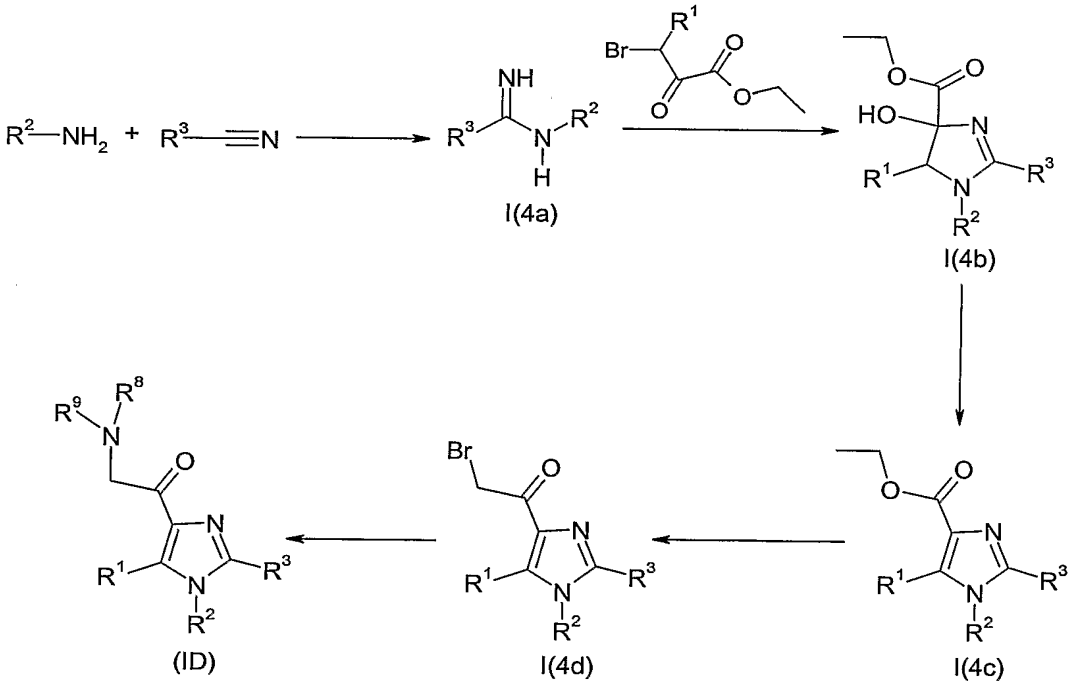


Scheme III

The N-protected amino compound I(3a) is cyclized to the morpholinyl derivative I(3b) by heating in the presence of a strong acid (e.g. 48% hydrogen bromide). The N-protecting group is then removed by heating in

the presence of 1-chloroethyl chloroformate and 1,8-bis(dimethylamino)naphthalene in 1,2-dichloroethane to produce a compound IC' (i.e., a compound of Formula (I) wherein L is -CH(OR^5)- or a compound of Formula (IC), where R^5 and R^8 form an ethylene bridge and R^9 is hydrogen). The morpholinyl nitrogen can then be alkylated by treating compound IC' with the appropriate aldehyde/ketone in the presence of sodium triacetoxyborohydride and acetic acid. Alternatively, the morpholinyl nitrogen may be acylated or sulfonated using standard procedures well-known to those skilled in the art. For example, compound IC' may be reacted with R^{10}(CH$_2$)$_m$C(O)Cl or R^{10}(CH$_2$)$_n$SO$_2$Cl (where m, n and R^{10} are as defined earlier) in the presence of triethylamine and an aprotic solvent (e.g., dichloromethane). Those compounds where R^9 or R^8 is -(CH$_2$)$_p$R^{10} (where p is 1, 2 or 3 and R^{10} is as defined earlier) may be produced by reducing the carbonyl of the corresponding acylated compound *via* standard reduction processes well-known to those skilled in the art.

Scheme IV below illustrates the preparation of imidazole derivatives.



Scheme IV

The benzamidine I(4a) is prepared by condensing the desired amine with the desired nitrile. The amine and nitrile are available from a variety of commercial sources or *via* simple modifications of commercially available materials using procedures well-known to those skilled in the art. One convenient means of achieving the condensation is by pre-treating the amine with trimethylaluminum prior to the addition of the nitrile and then heating the mixture to complete the reaction. The benzamidine I(4a) is then condensed with an appropriately substituted 3-bromo-2-oxo-propionic acid ethyl ester in the presence of a weak base (e.g., sodium bicarbonate) to form the hydroxy ester I(4b). The hydroxy ester I(4b) is then dehydrated to form the imidazole I(4c). The ester group of imidazole I(4c) is converted to the α-bromo ketone I(4d) by saponification of the ester using basic conditions such as lithium hydroxide in a mixture of methanol and water, reacting the intermediate acid with N,O-dimethylhydroxylamine hydrochloride and a suitable coupling agent, such as dicyclohexylcarbodiimide (DCC) or 1-propane phosphonic acid cyclic anhydride in an aprotic solvent (e.g.,THF). The intermediate N-methoxyamide is converted to the ketone by reacting with R^6R^7CH-metal (preferably, magnesium-halide (Grignard reagent) or lithium). The α-haloketone I(4d) is prepared using standard halogenation procedures well known to those skilled in the art (e.g., Br_2 in acetic acid). The α-bromo group can then be displaced with the desired amine to form the desired α-amine ketone (ID). For a more detailed description of the steps outlined in Scheme IV above, see Example 7 below.

Compound (ID) may be converted to imidazole derivatives wherein L is $-C(R^4)(OR^5)-$, where R^4 is hydrogen or (C_1-C_6)alkyl and R^5 is hydrogen, (C_1-C_6)alkyl, or taken together with R^8 or R^9 is $-CH_2CH_2-$ or $-CH_2C(O)-$ using the same general procedures described above for the synthesis of compounds of Formula (IB) and Formula (IC).

Conventional methods and/or techniques of separation and purification known to one of ordinary skill in the art can be used to isolate the

compounds of the present invention, as well as the various intermediates related thereto. Such techniques will be well-known to one of ordinary skill in the art and may include, for example, all types of chromatography (high pressure liquid chromatography (HPLC), column chromatography using common adsorbents such as silica gel, and thin-layer chromatography), recrystallization, and differential (i.e., liquid-liquid) extraction techniques.

The compounds of the present invention may be isolated and used *per se* or in the form of its pharmaceutically acceptable salt, solvate and/or hydrate. The term "salts" refers to inorganic and organic salts of a compound of the present invention. These salts can be prepared *in situ* during the final isolation and purification of a compound, or by separately reacting the compound, N-oxide, or prodrug with a suitable organic or inorganic acid and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, hydroiodide, sulfate, bisulfate, nitrate, acetate, trifluoroacetate, oxalate, besylate, palmitiate, pamoate, malonate, stearate, laurate, malate, borate, benzoate, lactate, phosphate, hexafluorophosphate, benzene sulfonate, tosylate, formate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactobionate, and laurylsulphonate salts, and the like. These may include cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, and the like, as well as non-toxic ammonium, quaternary ammonium, and amine cations including, but not limited to, ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. See, e.g., Berge, et al., *J. Pharm. Sci.*, **66**, 1-19 (1977).

The term "prodrug" means a compound that is transformed *in vivo* to yield a compound of Formula (I) or a pharmaceutically acceptable salt, hydrate or solvate of the compound. The transformation may occur by various mechanisms, such as through hydrolysis in blood. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in

Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

For example, if a compound of the present invention contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as (C_1-C_8)alkyl, (C_2-C_{12})alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C_1-C_2)alkylamino(C_2-C_3)alkyl (such as β-dimethylaminoethyl), carbamoyl-(C_1-C_2)alkyl, N,N-di(C_1-C_2)alkylcarbamoyl-(C_1-C_2)alkyl and piperidino-, pyrrolidino- or morpholino(C_2-C_3)alkyl.

Similarly, if a compound of the present invention contains an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as (C_1-C_6)alkanoyloxymethyl, 1-((C_1-C_6)alkanoyloxy)ethyl, 1-methyl-1-((C_1-C_6)alkanoyloxy)ethyl, (C_1-C_6)alkoxycarbonyloxymethyl, N-(C_1-C_6)alkoxycarbonylaminomethyl, succinoyl, (C_1-C_6)alkanoyl, α-amino(C_1-C_4)alkanoyl, arylacyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring L-amino acids, $P(O)(OH)_2$, $P(O)(O(C_1$-$C_6)alkyl)_2$ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate).

If a compound of the present invention incorporates an amine functional group, a prodrug can be formed by the replacement of a hydrogen atom in the amine group with a group such as R-carbonyl, RO-carbonyl, NRR'-carbonyl where R and R' are each independently (C_1-C_{10})alkyl, (C_3-

C_7)cycloalkyl, benzyl, or R-carbonyl is a natural α-aminoacyl or natural α-aminoacyl-natural α-aminoacyl, -C(OH)C(O)OY' wherein Y' is H, (C_1-C_6)alkyl or benzyl, -C(OY_0)Y_1 wherein Y_0 is (C_1-C_4) alkyl and Y_1 is (C_1-C_6)alkyl, carboxy(C_1-C_6)alkyl, amino(C_1-C_4)alkyl or mono-N- or di-N,N-(C_1-C_6)alkylaminoalkyl, -C(Y_2)Y_3 wherein Y_2 is H or methyl and Y_3 is mono-N- or di-N,N-(C_1-C_6)alkylamino, morpholino, piperidin-1-yl or pyrrolidin-1-yl.

The compounds of the present invention may contain asymmetric or chiral centers, and, therefore, exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of the present invention as well as mixtures thereof, including racemic mixtures, form part of the present invention. In addition, the present invention embraces all geometric and positional isomers. For example, if a compound of the present invention incorporates a double bond or a fused ring, both the *cis*- and *trans*- forms, as well as mixtures, are embraced within the scope of the invention. Both the single positional isomers and mixture of positional isomers resulting from the N-oxidation of the pyrimidine and pyrazine rings are also within the scope of the present invention.

Diastereomeric mixtures can be separated into their individual diastereoisomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereoisomers and converting (e.g., hydrolyzing) the individual diastereoisomers to the corresponding pure enantiomers. Also, some of the compounds of the present invention may be atropisomers (e.g., substituted biaryls) and are considered as part of this invention. Enantiomers can also be separated by use of a chiral HPLC column.

The compounds of the present invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as

water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms.

It is also possible that the compounds of the present invention may exist in different tautomeric forms, and all such forms are embraced within the scope of the invention. For example, all of the tautomeric forms of the imidazole and pyrazole moieties are included in the invention. Also, for example, all keto-enol and imine-enamine forms of the compounds are included in the invention.

The present invention also embraces isotopically-labeled compounds of the present invention which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine, iodine, and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, ^{123}I, and ^{36}Cl, respectively.

Certain isotopically-labeled compounds of the present invention (e.g., those labeled with ^{3}H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (i.e., ^{3}H) and carbon-14 (i.e., ^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased *in vivo* half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labeled compounds of the present invention can generally be prepared by following procedures analogous to those disclosed in the Schemes and/or in the Examples hereinbelow, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

Compounds of the present invention are useful for treating diseases, conditions and/or disorders modulated by cannabinoid receptor antagonists; therefore, another embodiment of the present invention is a pharmaceutical

composition comprising a therapeutically effective amount of a compound of the present invention and a pharmaceutically acceptable excipient, diluent or carrier.

A typical formulation is prepared by mixing a compound of the present invention and a carrier, diluent or excipient. Suitable carriers, diluents and excipients are well known to those skilled in the art and include materials such as carbohydrates, waxes, water soluble and/or swellable polymers, hydrophilic or hydrophobic materials, gelatin, oils, solvents, water, and the like. The particular carrier, diluent or excipient used will depend upon the means and purpose for which the compound of the present invention is being applied. Solvents are generally selected based on solvents recognized by persons skilled in the art as safe (GRAS) to be administered to a mammal. In general, safe solvents are non-toxic aqueous solvents such as water and other non-toxic solvents that are soluble or miscible in water. Suitable aqueous solvents include water, ethanol, propylene glycol, polyethylene glycols (e.g., PEG400, PEG300), etc. and mixtures thereof. The formulations may also include one or more buffers, stabilizing agents, surfactants, wetting agents, lubricating agents, emulsifiers, suspending agents, preservatives, antioxidants, opaquing agents, glidants, processing aids, colorants, sweeteners, perfuming agents, flavoring agents and other known additives to provide an elegant presentation of the drug (i.e., a compound of the present invention or pharmaceutical composition thereof) or aid in the manufacturing of the pharmaceutical product (i.e., medicament).

The formulations may be prepared using conventional dissolution and mixing procedures. For example, the bulk drug substance (i.e., compound of the present invention or stabilized form of the compound (e.g., complex with a cyclodextrin derivative or other known complexation agent)) is dissolved in a suitable solvent in the presence of one or more of the excipients described above. The compound of the present invention is typically formulated into pharmaceutical dosage forms to provide an easily controllable dosage of the drug and to give the patient an elegant and easily handleable product.

The pharmaceutical composition (or formulation) for application may be packaged in a variety of ways depending upon the method used for administering the drug. Generally, an article for distribution includes a container having deposited therein the pharmaceutical formulation in an appropriate form. Suitable containers are well-known to those skilled in the art and include materials such as bottles (plastic and glass), sachets, ampoules, plastic bags, metal cylinders, and the like. The container may also include a tamper-proof assemblage to prevent indiscreet access to the contents of the package. In addition, the container has deposited thereon a label that describes the contents of the container. The label may also include appropriate warnings.

The present invention further provides a method of treating diseases, conditions and/or disorders modulated by cannabinoid receptor antagonists in an animal that includes administering to an animal in need of such treatment a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition comprising an effective amount of a compound of the present invention and a pharmaceutically acceptable excipient, diluent, or carrier. The method is particularly useful for treating diseases, conditions and/or disorders modulated by cannabinoid receptor (in particular, CB1 receptor) antagonists.

Preliminary investigations have indicated that the following diseases, disorders and/or conditions are modulated by cannabinoid receptor antagonists: weight loss (e.g., reduction in calorie or food intake and/or appetite suppression), obesity, bulimia, depression, atypical depression, bipolar disorders, psychoses, schizophrenia, behavioral addictions, suppression of reward-related behaviors (e.g., conditioned place avoidance, such as suppression of cocaine- and morphine-induced conditioned place preference), alcoholism (e.g., alcohol abuse, addiction and/or dependence including abstinence, craving reduction and relapse prevention of alcohol intake), tobacco abuse (e.g., smoking addiction, cessation and/or dependence including craving reduction and relapse prevention of tobacco

smoking),, memory loss, Alzheimer's disease, dementia of aging, seizure disorders, epilepsy, gastrointestinal disorders (e.g., dysfunction of gastrointestinal motility or intestinal propulsion), and type II diabetes.

Accordingly, the compounds of the present invention described herein are useful in treating diseases, conditions, or disorders that are modulated by cannabinoid receptor antagonists. Consequently, the compounds of the present invention (including the compositions and processes used therein) may be used in the manufacture of a medicament for the therapeutic applications described herein.

Other diseases, conditions and/or disorders for which cannabinoid receptor antagonists may be effective include: premenstrual syndrome or late luteal phase syndrome, migraines, panic disorder, anxiety, post-traumatic syndrome, social phobia, attention deficit hyperactivity disorder, disruptive behavior disorders, impulse control disorders, borderline personality disorder, obsessive compulsive disorder, chronic fatigue syndrome, sexual dysfunction in males (e.g., premature ejaculation and erectile difficulty), sexual dysfunction in females, anorexia nervosa, disorders of sleep (e.g., sleep apnea), autism, mutism, neurodengenerative movement disorders (e.g., Parkinson's disease), spinal cord injury, damage of the central nervous system (e.g., trauma), stroke, neurodegenerative diseases or toxic or infective CNS diseases (e.g., encephalitis or meningitis), cardiovascular disorders (e.g., thrombosis), and diabetes insipidus.

The compounds of the present invention can be administered to a patient at dosage levels in the range of from about 0.7 mg to about 7,000 mg per day. For a normal adult human having a body weight of about 70 kg, a dosage in the range of from about 0.01 mg to about 100 mg per kilogram body weight is typically sufficient. However, some variability in the general dosage range may be required depending upon the age and weight of the subject being treated, the intended route of administration, the particular compound being administered and the like. The determination of dosage ranges and optimal dosages for a particular patient is well within the ability of

one of ordinary skill in the art having the benefit of the instant disclosure. It is also noted that the compounds of the present invention can be used in sustained release, controlled release, and delayed release formulations, which forms are also well known to one of ordinary skill in the art.

The compounds of this invention may also be used in conjunction with other pharmaceutical agents for the treatment of the diseases, conditions and/or disorders described herein. Therefore, methods of treatment that include administering compounds of the present invention in combination with other pharmaceutical agents are also provided. Suitable pharmaceutical agents that may be used in combination with the compounds of the present invention include anti-obesity agents such as apolipoprotein-B secretion/microsomal triglyceride transfer protein (apo-B/MTP) inhibitors, MCR-4 agonists, cholecystokinin-A (CCK-A) agonists, monoamine reuptake inhibitors (such as sibutramine), sympathomimetic agents, β_3 adrenergic receptor agonists, dopamine agonists (such as bromocriptine), melanocyte-stimulating hormone receptor analogs, 5HT2c agonists, melanin concentrating hormone antagonists, leptin (the OB protein), leptin analogs, leptin receptor agonists, galanin antagonists, lipase inhibitors (such as tetrahydrolipstatin, i.e. orlistat), anorectic agents (such as a bombesin agonist), Neuropeptide-Y antagonists, thyromimetic agents, dehydroepiandrosterone or an analog thereof, glucocorticoid receptor agonists or antagonists, orexin receptor antagonists, glucagon-like peptide-1 receptor agonists, ciliary neurotrophic factors (such as Axokine™ available from Regeneron Pharmaceuticals, Inc., Tarrytown, NY and Procter & Gamble Company, Cincinnati, OH), human agouti-related proteins (AGRP), ghrelin receptor antagonists, histamine 3 receptor antagonists or inverse agonists, neuromedin U receptor agonists and the like. Other anti-obesity agents, including the preferred agents set forth hereinbelow, are well known, or will be readily apparent in light of the instant disclosure, to one of ordinary skill in the art.

Especially preferred are anti-obesity agents selected from the group consisting of orlistat, sibutramine, bromocriptine, ephedrine, leptin, and pseudoephedrine. Preferably, compounds of the present invention and combination therapies are administered in conjunction with exercise and a sensible diet.

Representative anti-obesity agents for use in the combinations, pharmaceutical compositions, and methods of the invention can be prepared using methods known to one of ordinary skill in the art, for example, sibutramine can be prepared as described in U.S. Pat. No. 4,929,629; bromocriptine can be prepared as described in U.S. Pat. Nos. 3,752,814 and 3,752,888; and orlistat can be prepared as described in U.S. Pat. Nos. 5,274,143; 5,420,305; 5,540,917; and 5,643,874. All of the above recited U.S. patents are incorporated herein by reference.

Other suitable pharmaceutical agents that may be administered in combination with the compounds of the present invention include agents designed to treat tobacco abuse (e.g., nicotine partial agonists), agents to treat erectile dysfunction (e.g., dopaminergic agents, such as apomorphine), and agents to treat alcoholism, such as opioid antagonists (e.g., naltrexone (also known under the tradename ReVia™) and nalmefene) and acamprosate (also known under the tradename Campral™)). In addition, agents for reducing alcohol withdrawal symptoms may also be co-administered, such as benzodiazepines, beta-blockers, clonidine and carbamazepine. Treatment for alcoholism is preferably administered in combination with behavioral therapy including such components as motivational enhancement therapy, cognitive behavioral therapy, and referral to self-help groups, including Alcohol Anonymous (AA).

Other pharmaceutical agents that may be useful include antihypertensive agents; antidepressants; insulin and insulin analogs (e.g., LysPro insulin); GLP-1 (7-37) (insulinotropin) and GLP-1 (7-36)-NH_2; sulfonylureas and analogs thereof: chlorpropamide, glibenclamide, tolbutamide, tolazamide, acetohexamide, Glypizide®, glimepiride,

repaglinide, meglitinide; biguanides: metformin, phenformin, buformin; α2-antagonists and imidazolines: midaglizole, isaglidole, deriglidole, idazoxan, efaroxan, fluparoxan; other insulin secretagogues: linogliride, A-4166; glitazones: ciglitazone, Actos® (pioglitazone), englitazone, troglitazone, darglitazone, Avandia® (BRL49653); fatty acid oxidation inhibitors: clomoxir, etomoxir; α-glucosidase inhibitors: acarbose, miglitol, emiglitate, voglibose, MDL-25,637, camiglibose, MDL-73,945; β-agonists: BRL 35135, BRL 37344, RO 16-8714, ICI D7114, CL 316,243; phosphodiesterase inhibitors: L-386,398; lipid-lowering agents: benfluorex: fenfluramine; vanadate and vanadium complexes (e.g., Naglivan®) and peroxovanadium complexes; amylin antagonists; glucagon antagonists; gluconeogenesis inhibitors; somatostatin analogs; antilipolytic agents: nicotinic acid, acipimox, WAG 994, pramlintide (Symlin™), AC 2993, nateglinide, aldose reductase inhibitors (e.g., zopolrestat), glycogen phosphorylase inhibitors, sorbitol dehydrogenase inhibitors, sodium-hydrogen exchanger type 1 (NHE-1) inhibitors and/or cholesterol biosynthesis inhibitors or cholesterol absorption inhibitors, especially a HMG-CoA reductase inhibitor, or a HMG-CoA synthase inhibitor, or a HMG-CoA reductase or synthase gene expression inhibitor, a CETP inhibitor, a bile acid sequesterant, a fibrate, an ACAT inhibitor, a squalene synthetase inhibitor, an anti-oxidant or niacin. The compounds of the present invention may also be administered in combination with a naturally occurring compound that acts to lower plasma cholesterol levels. Such naturally occurring compounds are commonly called nutraceuticals and include, for example, garlic extract, *Hoodia* plant extracts, and niacin.

The dosage of the additional pharmaceutical agent will also be generally dependent upon a number of factors including the health of the subject being treated, the extent of treatment desired, the nature and kind of concurrent therapy, if any, and the frequency of treatment and the nature of the effect desired. In general, the dosage range of an anti-obesity agent is in the range of from about 0.001 mg to about 100 mg per kilogram body

weight of the individual per day, preferably from about 0.1 mg to about 10 mg per kilogram body weight of the individual per day. However, some variability in the general dosage range may also be required depending upon the age and weight of the subject being treated, the intended route of administration, the particular anti-obesity agent being administered and the like. The determination of dosage ranges and optimal dosages for a particular patient is also well within the ability of one of ordinary skill in the art having the benefit of the instant disclosure.

According to the methods of the invention, a compound of the present invention or a combination of a compound of the present invention and at least one additional pharmaceutical agent is administered to a subject in need of such treatment, preferably in the form of a pharmaceutical composition. In the combination aspect of the invention, the compound of the present invention and at least one other pharmaceutical agent may be administered either separately or in the pharmaceutical composition comprising both. It is generally preferred that such administration be oral. However, if the subject being treated is unable to swallow, or oral administration is otherwise impaired or undesirable, parenteral or transdermal administration may be appropriate.

According to the methods of the invention, when a combination of a compound of the present invention and at least one other pharmaceutical agent are administered together, such administration can be sequential in time or simultaneous with the simultaneous method being generally preferred. For sequential administration, a compound of the present invention and the additional pharmaceutical agent can be administered in any order. It is generally preferred that such administration be oral. It is especially preferred that such administration be oral and simultaneous. When a compound of the present invention and the additional pharmaceutical agent are administered sequentially, the administration of each can be by the same or by different methods.

According to the methods of the invention, a compound of the present invention or a combination of a compound of the present invention and at least one additional pharmaceutical agent (referred to herein as a "combination") is preferably administered in the form of a pharmaceutical composition. Accordingly, a compound of the present invention or a combination can be administered to a patient separately or together in any conventional oral, rectal, transdermal, parenteral, (for example, intravenous, intramuscular, or subcutaneous) intracisternal, intravaginal, intraperitoneal, intravesical, local (for example, powder, ointment or drop), or buccal, or nasal, dosage form.

Compositions suitable for parenteral injection generally include pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions, or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents, or vehicles include water, ethanol, polyols (propylene glycol, polyethylene glycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. Prevention of microorganism contamination of the compositions can be accomplished with various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example, sugars, sodium chloride, and the like. Prolonged absorption of injectable pharmaceutical compositions can be brought about by the use of agents capable of delaying absorption, for example, aluminum monostearate and gelatin.

Solid dosage forms for oral administration include capsules, tablets, powders, and granules. In such solid dosage forms, a compound of the present invention or a combination is admixed with at least one inert customary pharmaceutical excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders (e.g., starches, lactose, sucrose, mannitol, silicic acid and the like); (b) binders (e.g., carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, acacia and the like); (c) humectants (e.g., glycerol and the like); (d) disintegrating agents (e.g., agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, sodium carbonate and the like); (e) solution retarders (e.g., paraffin and the like); (f) absorption accelerators (e.g., quaternary ammonium compounds and the like); (g) wetting agents (e.g., cetyl alcohol, glycerol monostearate and the like); (h) adsorbents (e.g., kaolin, bentonite and the like); and/or (i) lubricants (e.g., talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate and the like). In the case of capsules and tablets, the dosage forms may also comprise buffering agents.

Solid compositions of a similar type may also be used as fillers in soft or hard filled gelatin capsules using such excipients as lactose or milk sugar, as well as high molecular weight polyethylene glycols, and the like.

Solid dosage forms such as tablets, dragees, capsules, and granules can be prepared with coatings and shells, such as enteric coatings and others well known in the art. They may also contain opacifying agents, and can also be of such composition that they release the compound of the present invention and/or the additional pharmaceutical agent in a delayed manner. Examples of embedding compositions that can be used are polymeric substances and waxes. The drug can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In

addition to the compound of the present invention or the combination, the liquid dosage form may contain inert diluents commonly used in the art, such as water or other solvents, solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (e.g., cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil, sesame seed oil and the like), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, or mixtures of these substances, and the like.

Besides such inert diluents, the composition can also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Suspensions, in addition to the compound of the present invention or the combination, may further comprise suspending agents, e.g., ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, and tragacanth, or mixtures of these substances, and the like.

Compositions for rectal or vaginal administration preferably comprise suppositories, which can be prepared by mixing a compound of the present invention or a combination with suitable non-irritating excipients or carriers, such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ordinary room temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity thereby releasing the active component(s).

Dosage forms for topical administration of the compounds of the present invention and combinations of the compounds of the present invention with anti-obesity agents may comprise ointments, powders, sprays and inhalants. The drugs are admixed under sterile condition with a pharmaceutically acceptable carrier, and any preservatives, buffers, or propellants that may be required. Ophthalmic formulations, eye ointments,

powders, and solutions are also intended to be included within the scope of the present invention.

The following paragraphs describe exemplary formulations, dosages, etc. useful for non-human animals. The administration of the compounds of the present invention and combinations of the compounds of the present invention with anti-obesity agents can be effected orally or non-orally (e.g., by injection).

An amount of a compound of the present invention or combination of a compound of the present invention with an anti-obesity agent is administered such that an effective dose is received. Generally, a daily dose that is administered orally to an animal is between about 0.01 and about 1,000 mg/kg of body weight, preferably between about 0.01 and about 300 mg/kg of body weight.

Conveniently, a compound of the present invention (or combination) can be carried in the drinking water so that a therapeutic dosage of the compound is ingested with the daily water supply. The compound can be directly metered into drinking water, preferably in the form of a liquid, water-soluble concentrate (such as an aqueous solution of a water-soluble salt).

Conveniently, a compound of the present invention (or combination) can also be added directly to the feed, as such, or in the form of an animal feed supplement, also referred to as a premix or concentrate. A premix or concentrate of the compound in a carrier is more commonly employed for the inclusion of the agent in the feed. Suitable carriers are liquid or solid, as desired, such as water, various meals such as alfalfa meal, soybean meal, cottonseed oil meal, linseed oil meal, corncob meal and corn meal, molasses, urea, bone meal, and mineral mixes such as are commonly employed in poultry feeds. A particularly effective carrier is the respective animal feed itself; that is, a small portion of such feed. The carrier facilitates uniform distribution of the compound in the finished feed with which the premix is blended. Preferably, the compound is thoroughly blended into the premix and, subsequently, the feed. In this respect, the compound may be

dispersed or dissolved in a suitable oily vehicle such as soybean oil, corn oil, cottonseed oil, and the like, or in a volatile organic solvent and then blended with the carrier. It will be appreciated that the proportions of compound in the concentrate are capable of wide variation since the amount of the compound in the finished feed may be adjusted by blending the appropriate proportion of premix with the feed to obtain a desired level of compound.

High potency concentrates may be blended by the feed manufacturer with proteinaceous carrier such as soybean oil meal and other meals, as described above, to produce concentrated supplements, which are suitable for direct feeding to animals. In such instances, the animals are permitted to consume the usual diet. Alternatively, such concentrated supplements may be added directly to the feed to produce a nutritionally balanced, finished feed containing a therapeutically effective level of a compound of the present invention. The mixtures are thoroughly blended by standard procedures, such as in a twin shell blender, to ensure homogeneity.

If the supplement is used as a top dressing for the feed, it likewise helps to ensure uniformity of distribution of the compound across the top of the dressed feed.

Drinking water and feed effective for increasing lean meat deposition and for improving lean meat to fat ratio are generally prepared by mixing a compound of the present invention with a sufficient amount of animal feed to provide from about 10^{-3} to about 500 ppm of the compound in the feed or water.

The preferred medicated swine, cattle, sheep and goat feed generally contain from about 1 to about 400 grams of a compound of the present invention (or combination) per ton of feed, the optimum amount for these animals usually being about 50 to about 300 grams per ton of feed.

The preferred poultry and domestic pet feeds usually contain about 1 to about 400 grams and preferably about 10 to about 400 grams of a compound of the present invention (or combination) per ton of feed.

For parenteral administration in animals, the compounds of the present invention (or combination) may be prepared in the form of a paste or a pellet and administered as an implant, usually under the skin of the head or ear of the animal in which increase in lean meat deposition and improvement in lean meat to fat ratio is sought.

In general, parenteral administration involves injection of a sufficient amount of a compound of the present invention (or combination) to provide the animal with about 0.01 to about 20 mg/kg/day of body weight of the drug. The preferred dosage for poultry, swine, cattle, sheep, goats and domestic pets is in the range of from about 0.05 to about 10 mg/kg/day of body weight of drug.

Paste formulations can be prepared by dispersing the drug in a pharmaceutically acceptable oil such as peanut oil, sesame oil, corn oil or the like.

Pellets containing an effective amount of a compound of the present invention, pharmaceutical composition, or combination can be prepared by admixing a compound of the present invention or combination with a diluent such as carbowax, carnuba wax, and the like, and a lubricant, such as magnesium or calcium stearate, can be added to improve the pelleting process.

It is, of course, recognized that more than one pellet may be administered to an animal to achieve the desired dose level which will provide the increase in lean meat deposition and improvement in lean meat to fat ratio desired. Moreover, implants may also be made periodically during the animal treatment period in order to maintain the proper drug level in the animal's body.

The present invention has several advantageous veterinary features. For the pet owner or veterinarian who wishes to increase leanness and/or trim unwanted fat from pet animals, the instant invention provides the means by which this may be accomplished. For poultry and swine breeders,

utilization of the method of the present invention yields leaner animals that command higher sale prices from the meat industry.

Embodiments of the present invention are illustrated by the following Examples. It is to be understood, however, that the embodiments of the invention are not limited to the specific details of these Examples, as other variations thereof will be known, or apparent in light of the instant disclosure, to one of ordinary skill in the art.

EXAMPLES

Unless specified otherwise, starting materials are generally available from commercial sources such as Aldrich Chemicals Co. (Milwaukee, WI), Lancaster Synthesis, Inc. (Windham, NH), Acros Organics (Fairlawn, NJ), Maybridge Chemical Company, Ltd. (Cornwall, England), Tyger Scientific (Princeton, NJ), and AstraZeneca Pharmaceuticals (London, England).

General Experimental Procedures

NMR spectra were recorded on a Varian Unity™ 400 (available from Varian Inc., Palo Alto, CA) at room temperature at 400 MHz for proton. Chemical shifts are expressed in parts per million (δ) relative to residual solvent as an internal reference. The peak shapes are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad singlet; 2s, two singlets. Atmospheric pressure chemical ionization mass spectra (APCI) were obtained on a Fisons™ Platform II Spectrometer (carrier gas: acetonitrile: available from Micromass Ltd, Manchester, UK). Chemical ionization mass spectra (CI) were obtained on a Hewlett-Packard™ 5989 instrument (ammonia ionization, PBMS: available from Hewlett-Packard Company, Palo Alto, CA). Electrospray ionization mass spectra (ES) were obtained on a Waters™ ZMD instrument (carrier gas: acetonitrile: available from Waters Corp., Milford, MA). Where the intensity of chlorine or bromine-containing ions are described, the expected intensity ratio was observed (approximately 3:1 for $^{35}Cl/^{37}Cl$-containing ions and 1:1 for $^{79}Br/^{81}Br$-containing ions) and the intensity of only the lower mass ion is given. In some cases only representative ^{1}H NMR peaks are given. MS peaks are reported for all

examples. Optical rotations were determined on a PerkinElmer™ 241 polarimeter (available from PerkinElmer Inc., Wellesley, MA) using the sodium D line (λ = 589 nm) at the indicated temperature and are reported as follows $[\alpha]_D^{temp}$, concentration (c = g/100 ml), and solvent.

Column chromatography was performed with either Baker™ silica gel (40 μm; J.T. Baker, Phillipsburg, NJ) or Silica Gel 50 (EM Sciences™, Gibbstown, NJ) in glass columns or in Flash 40 Biotage™ columns (ISC, Inc., Shelton, CT) under low nitrogen pressure.

Example 1 provides general procedures for preparing compounds of Formula (I) where L is a carbonyl.

Example 1

N-Methoxy-N-methyl-5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide (I-1a):

Isopropylmagnesium chloride (15 ml, 30 mmol) was added dropwise over a 10 to 15 minute period to a stirred solution of ethyl 5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazole-3-carboxylate (8.15 g, 21.7 mmol) and N,O-dimethylhydroxylamine hydrochloride (1.51 g, 15.5 mmol) in THF at -25°C. After stirring for an additional 15 minutes at –25 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl and then extracted with methyl-*tert*-butyl ether. The organic layer was washed with brine, dried over sodium sulfate and concentrated *in vacuo* to give the title compound I-1a as a golden oil (8.76 g).

1-[5-(4-Chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-ethanone(I-1b):

Methylmagnesium bromide (10 ml, 30.4 mmol) was added dropwise to a stirred solution of N-methoxy-N-methyl-5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide I-1a (8.48 g, 21.7 mmol) in THF (100 ml) at -10°C. The reaction mixture was stirred for another 15 minutes at –10 °C to afford a yellow solution which became slurry within 30 minutes. The reaction mixture was warmed up to 0 °C over a period of 30

minutes, quenched with NH_4Cl and diluted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, and concentrated *in vacuo* to give the title compound I-1b as a light-yellow colored solid (7.52 g).

2-Bromo-1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-ethanone(I-1c):

Copper (II) bromide (12.9 g, 58.0 mmol) was added to a solution of 1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-ethanone I-1b in 1:1 ethyl acetate/methylene chloride (400 ml). The reaction mixture was heated in an oil bath to reflux for 2.5 hours. The reaction was monitored by ^{1}HNMR/LCMS. The reaction mixture was removed from the oil bath and filtered through a Celite® pad and then washed with ethyl acetate (1 L). The filtrate was partitioned with 200 ml H_2O. The organic layer was separated, dried over sodium sulfate, and concentrated *in vacuo*. The resulting solids were purified by chromatography (25%-35% methylene chloride/hexanes, silica) to give the title compound I-1c (8.91 g).

General procedure for the preparation of a compound of Formula (I) where L is -C(O)-.

A solution of 2-bromo-1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-ethanone I-1c (130 mg, 0.307 mmol) in dichloromethane (1 ml) was treated with the appropriate amine (0.398 mmol) and diisopropylethylamine (70 μL, 0.4 mmol) at room temperature. The reaction mixture was stirred overnight at room temperature and then diluted with methylene chloride, washed with half saturated sodium bicarbonate, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel chromatography to afford the appropriate aminoketone.

Table I lists compounds that were prepared using the general procedures described above with the appropriate starting materials.

Table I

Example No.	Compound Name	LCMS m/z (M + 1)
1A-1	2-(Benzyl-isopropyl-amino)-1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-ethanone hydrochloride salt	492.2
1A-2	1-[5-(4-Chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-(5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]- ethanone formate salt	574.1
1A-3	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(2,6-dimethyl-morpholin-4-yl)-ethanone formate salt	457.9
1A-4	1-{2-[1-(2-Chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-4-phenyl-piperidine-4-carbonitrile formate salt	529.1
1A-5	2-(4-Acetyl-4-phenyl-piperidin-1-yl)-1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-ethanone formate salt	546.1
1A-6	1-[5-(4-Chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(3,3-dimethylpiperidin-1-yl)-ethanone formate salt	456.0
1A-7	1-[1-(2-Chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(2,6-dimethylpiperidin-1-yl)-ethanone formate salt	456.1
1A-8	1-[5-(4-Chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-(3-trifluoromethylpyridin-2-yl)-piperazin-1-yl]- ethanone formate salt	574.1
1A-9	2-(4-Benzyl-[1,4]diazepan-1-yl)-1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-ethanone formate salt	532.9
1A-10	1-[1-(2-Chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(2-methoxymethyl-pyrrolidin-1-yl)-ethanone formate salt	458.1
1A-11	1-[1-(2-Chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl)-ethanone formate salt	442.1
1A-12	1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(ethyl-[1,3,4]thiadiazol-2-yl-amino)-ethanone formate salt	458.5
1A-13	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]- 2-[3-(3-methoxy-phenyl)-piperidin-1-yl]-ethanone	534.1
1A-14	1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]- -(3-hydroxy-3-o-tolyl-pyrrolidin-1-yl)-ethanone	520.1

Example No.	Compound Name	LCMS m/z (M + 1)
1A-15	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]- 2-[4-(4-methyl-4H-[1,2,4]triazol-3-yl)-piperidin-1-yl]- ethanone.	509.1
1A-16	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]- 2-[4-(3,4-dihydro-1H-isoquinolin-2-yl)-piperidin-1-yl]- ethanone	559.2
1A-17	1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]- 2-(4-hydroxy-4-phenyl-octahydro-quinolin-1-yl)-ethanone	574.1
1A-18	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]- -(4-trifluoromethyl-10-aza-tricyclo[6.3.1.0]dodeca-2,4,6-trien-10-yl)-ethanone	570.0
1A-19	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]- 2-[methyl-(5-phenyl-1H-pyrazol-3-ylmethyl)-amino]-ethanone	529.1
1A-20	1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]- 2-[methyl-(1-pyridin-4-yl-ethyl)-amino]-ethanone	479.6
1A-21	1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]- 2-[methyl-(1-pyridin-3-yl-ethyl)-amino]-ethanone	479.1
1A-22	1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(3-phenyl-piperidin-1-yl)-ethanone	504.2
1A-23	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(4-pyrimidin-2-yl-[1,4]diazepan-1-yl)-ethanone	521.1
1A-24	N-(1-{2-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-pyrrolidin-3-yl)-N-methyl-acetamide	485.7
1A-25	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(2,3-dihydro-5H-benzo[f][1,4]oxazepin-4-yl)-ethanone	492.7
1A-26	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]- 2-[methyl-(1-methyl-1H-pyrazol-4-ylmethyl)-amino]-ethanone	468.7
1A-27	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]- 2-(1,1-dioxo-thiazolidin-3-yl)-ethanone	464.1
1A-28	1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-spiro[isobenzofuran-1(3H),4'-piperidin-1'-yl-ethanone	532.1

Example No.	Compound Name	LCMS m/z (M + 1)
1A-29	1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(methyl-pyridin-2-ylmethyl-amino)-ethanone	465.7
1A-30	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-({4-[ethyl-(2-hydroxy-ethyl)-amino]-butyl}-methyl-amino)-ethanone	518.0
1A-31	1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[3-(3-methoxy-phenyl)-3-propyl-pyrrolidin-1-yl]-ethanone	562.2
1A-32	1-{2-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-4-phenyl-piperidine-4-carbonitrile hydrochloride salt	528.9
1A-33	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(3,3-dimethyl-piperidin-1-yl)-ethanone hydrochloride salt	456.0
1A-34	1-[5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(3,3-dimethylpiperidin-1-yl)-ethanone	489.9
1A-35	1-{2-[5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-4-phenyl-piperidine-4-carbonitrile	562.8
1A-36	1-{2-[5-(4-chlorophenyl)-1-(2-fluoro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-4-phenyl-piperidine-4-carbonitrile	512.9
1A-37	1-[5-(4-chlorophenyl)-1-(2-fluoro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-(3,3-dimethyl-piperidin-1-yl)-ethanone	440.0
1A-38	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(3,3-dimethylpiperidin-1-yl)-2-methyl-propan-1-one	484.4
1A-39	1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-isopropylamino-2-methyl-propan-1-one	430.2
1A-40	2-[(1-Benzyl-cyclopentyl)-methyl-amino]-1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-ethanone	532.8
1A-41	1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(5-methyl-1,3,4,5-tetrahydro-pyrido[4,3-b]indol-2-yl)-ethanone	528.8
1A-42	1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[isopropyl-(2-phenoxy-ethyl)-amino]-ethanone	522.8

Example No.	Compound Name	LCMS m/z (M + 1)
1A-43	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[2-(1H-indol-3-yl)-pyrrolidin-1-yl]-ethanone	529.8
1A-44	2-(4-Benzoyl-piperazin-1-yl)-1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-ethanone	535.5
1A-45	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-(furan-2-carbonyl)-piperazin-1-yl]-ethanone	525.5
1A-46	1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[methyl-(1,2,3,4-tetrahydro-naphthalen-1-yl)-amino]- ethanone	504.8
1A-47	2-(Benzyl-bicyclo[2.2.1]hept-2-yl-amino)-1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-ethanone	544.8
1A-48	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(3,5-dimethyl-piperidin-1-yl)-ethanone	456.8
1A-49	2-(1-Aza-spiro[4.5]dec-1-yl)-1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-ethanone	482.8
1A-50	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(4-phenyl-piperidin-1-yl)-ethanone	504.8
1A-51	4-{2-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-piperazine-1-carboxylic acid 2-hydroxy-2-methyl-propyl ester	545.9
1A-52	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-(tetrahydro-furan-2-ylmethyl)-piperazin-1-yl]-ethanone	515.5
1A-53	3-{2-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-2,3,4,4a-tetrahydro-1H-3,9a-diaza-fluoren-9-one	533.5
1A-54	2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-ethanone	562.8
1A-55	2-[(1-Benzyl-pyrrolidin-3-ylmethyl)-methyl-amino]-1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-ethanone	549.5
1A-56	2-(3-Benzylamino-8-aza-bicyclo[3.2.1]oct-8-yl)-1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-ethanone	561.5

Example No.	Compound Name	LCMS m/z (M + 1)
1A-57	1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(1-p-tolyl-3-aza-bicyclo[3.1.0]hex-3-yl)-ethanone	516.8
1A-58	1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethanone	506.8
1A-59	2-[Benzyl-(2-hydroxymethyl-cyclohexyl)-amino]-1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-ethanone	562.8
1A-60	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(3-hydroxymethyl-3,4-dihydro-1H-isoquinolin-2-yl)-ethanone	506.8
1A-61	2-({2-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-ethyl-amino)-isonicotinonitrile	490.7
1A-62	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[(2,6-dichloro-benzyl)-(3-hydroxypropyl)-amino]-ethanone	576.8
1A-63	2-[Benzyl-(2-hydroxy-cyclobutyl)-amino]-1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-ethanone	520.8
1A-64	2-(4-Benzo[d]isoxazol-3-yl-piperazin-1-yl)-1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-ethanone	546.8
1A-65	1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(3,4-dihydro-6-methoxyspiro[naphthalene-1(2H),4'-piperidin-1'-yl-ethanone	574.9
1A-66	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[3-(pyrrolidine-1-carbonyl)-piperidin-1-yl]-ethanone	525.8
1A-67	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]- 2-(3-methyl-3-phenyl-piperidin-1-yl)-ethanone	536.5
1A-68	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]- 2-[4-(pyridine-4-carbonyl)-piperazin-1-yl]-ethanone	536.5
1A-69	6-(4-{2-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-piperazin-1-yl)-nicotinonitrile	531.8

Example No.	Compound Name	LCMS m/z (M + 1)
1A-70	5-{2-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-2,5-diaza-bicyclo[2.2.1]heptane-2-carboxylic acid tert-butyl ester	542.1
1A-71	1-{2-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-4-cyclohexylamino-piperidine-4-carboxylic acid amide	569.2
1A-72	1-{2-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-4-isopropylamino-piperidine-4-carboxylic acid amide	530.6
1A-73	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(4-pyrimidin-2-yl-piperazin-1-yl)-ethanone	507.8
1A-74	1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(methyl-pyridin-4-ylmethyl-amino)-ethanone	465.7
1A-75	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(4-quinoxalin-2-yl-piperazin-1-yl)-ethanone	557.8
1A-76	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-(5-chloro-pyridin-2-yl)-piperazin-1-yl]-ethanone	540.8
1A-77	1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(10-oxa-4-aza-tricyclo[5.2.1.0]dec-4-yl)-ethanone	482.8
1A-78	1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[(1,1-dioxo-tetrahydro-1&-thiophen-3-yl)-methyl-amino]-ethanone	492.7
1A-79	1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[(2-hydroxy-1-methyl-2-phenyl-ethyl)-methyl-amino]-ethanone	508.8
1A-80	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(3-hydroxy-piperidin-1-yl)-ethanone	444.7
1A-81	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-piperidin-1-yl-ethanone	428.7
1A-82	1-{2-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-1,1-dimethyl-2-oxo-ethyl}-4-phenyl-piperidine-4-carbonitrile	557.3
1A-83	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-cyclohexylamino-ethanone	442.3

Example No.	Compound Name	LCMS m/z (M + 1)
1A-84	2-Benzylamino-1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-ethanone hydrochloride salt	450.2
1A-85	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-(furan-2-carbonyl)-piperazin-1-yl]-ethanone hydrochloride salt	523.2
1A-86	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-(4-methyl-4H-[1,2,4]triazol-3-yl)-piperidin-1-yl]-ethanone hydrochloride salt	509.2
1A-87	1-{2-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-4-isopropylamino-piperidine-4-carboxylic acid amide hydrochloride salt	528.3
1A-88	1-[5-(4-Chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(2-phenylpiperidin-1-yl)-ethanone	504.9
1A-89	4-{2-[5-(4-Chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-piperazine-1-carboxylic acid isobutyl ester	530.1
1A-90	2-[4-(Benzofuran-2-carbonyl)-piperazin-1-yl]-1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-ethanone	573.9
1A-91	1'-{2-[1-(2-Chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-[1,4']bipiperidinyl-4'-carboxylic acid amide	555.2
1A-92	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[methyl-(1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-amino]-ethanone	518.9
1A-93	3-{2-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one	533.9
1A-94	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-(2-phenyl-[1,3]dioxolan-2-yl)-piperidin-1-yl]-ethanone.	576.9
1A-95	1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(cyclohexyl-pyridin-4-yl-amino)-ethanone	519.9
1A-96	1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[(4-hydroxy-1,1-dioxo-tetrahydro-1-thiophen-3-yl)-isopropyl-amino]-ethanone	538.6

Example No.	Compound Name	LCMS m/z (M + 1)
1A-97	(3-{2-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-3-aza-bicyclo[3.1.0]hex-6-yl)-carbamic acid methyl ester	499.8
1A-98	1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-(4-fluoro-phenyl)-4-hydroxy-piperidin-1-yl]-ethanone	538.9
1A-99	1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(3-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-ethanone	490.8
1A-100	1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(2,3-dihydrospiro[1H-indene-1,4'-piperinin]-1'-yl-ethanone	531.2
1A-101	1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-spiro[1H-indene-1,4'-piperinin]-1'-yl-ethanone	528.9
1A-102	1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(3-cyclohexyl-piperidin-1-yl)-ethanone	511.2
1A-103	1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(3-trifluoromethyl-10-aza-tricyclo[6.3.1.0]dodeca-2(7),3,5-trien-10-yl)-ethanone	570.8
1A-104	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(4-cyclopentyl-piperazin-1-yl)-ethanone	497.9
1A-105	1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(3-pyrrol-1-ylmethyl-piperidin-1-yl)-ethanone	507.9
1A-106	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(4-phenyl-azepan-1-yl)-ethanone	519.1
1A-107	1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[cyclopentyl-(2-hydroxy-ethyl)-amino]-ethanone	472.8
1A-108	1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[2-(4-fluoro-phenyl)-pyrrolidin-1-yl]-ethanone	508.8
1A-109	1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[2-(2-methyl-pyridin-4-yl)-pyrrolidin-1-yl]-ethanone	507.5
1A-110	(1-{2-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-piperidin-4-yl)-carbamic acid tert-butyl ester	543.9

Example No.	Compound Name	LCMS m/z (M + 1)
1A-111	(1-{2-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-piperidin-4-yl)-methyl-carbamic acid tert-butyl ester	557.9
1A-112	2-(2-Benzyl-piperidin-1-yl)-1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-ethanone	518.9
1A-113	2-[Benzyl-(2-hydroxymethyl-cyclohexyl)-amino]-1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-ethanone	563.0
1A-114	4-{2-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-[1,4]diazepane-1-carboxylic acid tert-butyl ester	543.9
1A-115	1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(1,3-dihydro-isoindol-2-yl)-ethanone	462.8
1A-116	2-(4-Benzyl-piperidin-1-yl)-1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-ethanone	518.9
1A-117	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[3-(3,5-dimethyl-pyrazol-1-yl)-4-hydroxy-pyrrolidin-1-yl]-ethanone	525.1
1A-118	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-ethanone	487.0
1A-119	1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[cyclopentyl-(2-methoxy-ethyl)-amino]-ethanone	486.9
1A-120	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(1-methyl-10-oxa-4-aza-tricyclo[5.2.1.0]dec-4-yl)-ethanone	496.8
1A-121	1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(2,5-dimethyl-pyrrolidin-1-yl)-ethanone	442.8
1A-122	4-{2-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-3,5-dimethyl-piperazine-1-sulfonic acid dimethylamide	564.9
1A-123	2-(4-Benzyl-[1,4]diazepan-1-yl)-1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-ethanone	535.6
1A-124	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-(5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-ethanone	574.9

Example No.	Compound Name	LCMS m/z (M + 1)
1A-125	N-(1-{2-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-pyrrolidin-3-yl)-N-methyl-acetamide	486.1
1A-126	4-{2-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-piperazine-1-sulfonic acid dimethylamide	537.1
1A-127	1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(1-ethyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-ethanone	494.1
1A-128	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-(2,6-dimethyl-morpholin-4-yl)-piperidin-1-yl]-ethanone	543.6
1A-129	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[methyl-(2-pyridin-2-yl-ethyl)-amino]-ethanone	479.8
1A-130	4-(1-{2-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-piperidin-4-yloxy)-2-fluoro-benzonitrile	563.9
1A-131	2-(4-Acetyl-piperazin-1-yl)-1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-ethanone	471.8
1A-132	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(2-methyl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-ethanone	492.8
1A-133	1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(2-cyclopropyl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-ethanone	519.1
1A-134	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-(6-methoxy-pyridazin-3-yl)-piperazin-1-yl]-ethanone	537.9
1A-135	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[3-(4-methyl-4H-[1,2,4]triazol-3-yl)-piperidin-1-yl]-ethanone	511.6
1A-136	(1-{2-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-4-methyl-piperidin-3-yl)-carbamic acid tert-butyl ester	558.0
1A-137	1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(1-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-ethanone	480.0
1A-138	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(4-m-tolyloxy-piperidin-1-yl)-ethanone	534.9

Example No.	Compound Name	LCMS m/z (M + 1)
1A-139	2-[4-(1-{2-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-piperidin-4-yloxy)-phenyl]-acetamide	577.9
1A-140	1-{2-[5-(4-chlorophenyl)-1-(2-fluoro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-4-isopropylamino-piperidine-4-carboxylic acid amide hydrochloride salt	512.3
1A-141	1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(4-ethoxy-piperidin-1-yl)-ethanone	472.8
1A-142	1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(cyclohexyl-pyridin-2-yl-amino)-ethanone	519.9
1A-143	4-{2-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-piperazine-1-carboxylic acid tert-butyl ester	529.2
1A-144	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-piperazin-1-yl-ethanone hydrochloride salt	429.2
1A-145	1-{2-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-azetidine-3-carboxylic acid methyl ester	490.3
1A-146	1-[5-(4-chlorophenyl)-1-(2-fluoro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-(furan-2-carbonyl)-piperazin-1-yl]-ethanone hydrochloride salt	507.2
1A-147	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(4-cyclopentanecarbonyl-piperazin-1-yl)-ethanone	525.3
1A-148	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-(5-methyl-1H-pyrazole-3-carbonyl)-piperazin-1-yl]-ethanone hydrochloride salt	537.2
1A-149	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-(pyridine-2-carbonyl)-piperazin-1-yl]-ethanone	534.3
1A-150	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]- 2-[4-(pyrazine-2-carbonyl)-piperazin-1-yl]-ethanone	535.2
1A-151	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-piperidin-1-yl-ethanone. hydrochloride salt	428.1

Example No.	Compound Name	LCMS m/z (M + 1)
1A-152	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(4-pyrimidin-2-yl-piperazin-1-yl)-ethanone hydrochloride salt	507.1
1A-153	2-(4-Benzoyl-piperazin-1-yl)-1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-ethanone hydrochloride salt	533.1
1A-154	1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(4-methanesulfonyl-piperazin-1-yl)-ethanone	507.1
1A-155	1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-(propane-2-sulfonyl)-piperazin-1-yl]-ethanone	535.2
1A-156	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(4-trifluoroacetyl-piperazin-1-yl)-ethanone	525.2
1A-157	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(4-hydroxy-piperidin-1-yl)-ethanone	444.6
1A-158	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-morpholin-4-yl-ethanone	430.2
1A-159	1-{2-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-piperidine-4-carboxylic acid dimethylamide	499.3
1A-160	1-{2-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-piperidine-4-carboxylic acid ethylamide	499.3
1A-161	1-{2-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-piperidine-4-carboxylic acid cyclopentylamide	539.8
1A-162	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-(3-hydroxymethyl-piperidine-1-carbonyl)-piperidin-1-yl]-ethanone	569.8
1A-163	1-{2-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-piperidine-4-carboxylic acid amide	471.7
1A-164	1-(1-{2-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-piperidin-4-yl)-pyrrolidin-2-one	511.8
1A-165	8-{2-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-1-isopropyl-1,3,8-triaza-spiro[4.5]decan-4-one	540.8

Example No.	Compound Name	LCMS m/z (M + 1)
1A-166	3-(Benzyl-{2-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-amino)-propionitrile	503.8
1A-167	Cyclopentanecarboxylic acid (1-{2-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-piperidin-4-yl)-amide	539.8
1A-168	2-(4-Acetyl-[1,4]diazepan-1-yl)-1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-ethanone	485.8
1A-169	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[3-(4-fluoro-phenoxy)-azetidin-1-yl]-ethanone	510.2
1A-170	1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-(4-trifluoromethyl-pyrimidin-2-yl)-piperazin-1-yl]-ethanone	575.8
1A-171	4-{2-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-piperazine-1-sulfonic acid dimethylamide hydrochloride salt	536.2
1A-172	2-(4-Amino-piperidin-1-yl)-1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-ethanone hydrochloride salt	443.3
1A-173	4-{2-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-piperazine-1-carboxylic acid isobutyl ester hydrochloride salt	529.3
1A-174	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-(thiophene-3-carbonyl)-piperazin-1-yl]-ethanone	539.1
1A-175	2-(4-{2-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-piperazine-1-1A-carbonyl)-pyrrolidine-1-carbaldehyde	554.1
1A-176	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-(5-methyl-isoxazole-3-carbonyl)-piperazin-1-yl]-ethanone	538.0
1A-177	1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(4-ethoxyacetyl-piperazin-1-yl)-ethanone	515.1
1A-178	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-(1,5-dimethyl-1H-pyrazole-3-carbonyl)-piperazin-1-yl]-ethanone	551.1
1A-179	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-([1,2,3]thiadiazole-4-carbonyl)-piperazin-1-yl]-ethanone	541.0

Example No.	Compound Name	LCMS m/z (M + 1)
1A-180	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-(5-methyl-isoxazole-4-carbonyl)-piperazin-1-yl]-ethanone	538.1
1A-181	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-(thiazole-4-carbonyl)-piperazin-1-yl]-ethanone	540.0
1A-182	4-(4-{2-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-piperazine-1-carbonyl)-1-methyl-pyrrolidin-2-one	554.1
1A-183	4-(4-{2-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-piperazine-1-carbonyl)-benzonitrile	558.1
1A-184	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-(furan-3-carbonyl)-piperazin-1-yl]-ethanone	523.2
1A-185	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-(1-methyl-1H-pyrrole-2-carbonyl)-piperazin-1-yl]- ethanone	536.1
1A-186	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-(isoxazole-3-carbonyl)-piperazin-1-yl]-ethanone	524.1
1A-187	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-(2-methyl-2H-pyrazole-3-carbonyl)-piperazin-1-yl]-ethanone	537.1
1A-188	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-(5-methyl-1H-pyrazole-3-carbonyl)-piperazin-1-yl]-ethanone	537.1
1A-189	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-(tetrahydro-furan-2-carbonyl)-piperazin-1-yl]-ethanone	527.2
1A-190	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(4-methoxyacetyl-piperazin-1-yl)-ethanone	501.1
1A-191	2-[4-(5-Chloro-furan-2-carbonyl)-piperazin-1-yl]-1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-ethanone	559.0
1A-192	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-(isothiazole-4-carbonyl)-piperazin-1-yl]-ethanone	540.1
1A-193	N-[2-(4-{2-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-piperazin-1-yl)-2-oxo-ethyl]-acetamide	528.1

Example No.	Compound Name	LCMS m/z (M + 1)
1A-194	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-(tetrahydro-pyran-4-carbonyl)-piperazin-1-yl]-ethanone	541.2
1A-195	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-{4-[(5-methylpyrazol-1-yl)-acetyl]-piperazin-1-yl}-ethanone	551.1
1A-196	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(4-cyclopropanecarbonyl-piperazin-1-yl)-ethanone	497.1
1A-197	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-(1-methyl-cyclopropanecarbonyl)-piperazin-1-yl]-ethanone	511.1
1A-198	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-(5-methyl-[1,3,4]oxadiazole-2-carbonyl)-piperazin-1-yl]-ethanone	539.1
1A-199	5-(4-{2-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-piperazine-1-carbonyl)-pyrrolidin-2-one	540.1
1A-200	N-(1-{2-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-piperidin-4-yl)-2,2,2-trifluoro-acetamide	539.1
1A-201	N-(1-{2-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-piperidin-4-yl)-methanesulfonamide	521.2
1A-202	N-(1-{2-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-piperidin-4-yl)-2-ethoxy-acetamide	529.3
1A-203	1-Methyl-5-oxo-pyrrolidine-3-carboxylic acid (1-{2-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-piperidin-4-yl)-amide	568.3
1A-204	5-Methyl-isoxazole-4-carboxylic acid (1-{2-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-piperidin-4-yl)-amide	552.3
1A-205	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(4-trifluoroacetyl-piperazin-1-yl)-ethanone hydrochloride salt	525.2
1A-206	4-{2-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-piperazine-1-carboxylic acid pyrazol-1-ylmethyl ester	553.3
1A-207	Tetrahydro-pyran-4-carboxylic acid (1-{2-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-piperidin-4-yl)-amide	555.1

Example No.	Compound Name	LCMS m/z (M + 1)
1A-208	N-(1-{2-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-piperidin-4-yl)-2-(5-methyl-pyrazol-1-yl)-acetamide	565.2
1A-209	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-(4-fluoro-benzoyl)-piperazin-1-yl]-ethanone hydrochloride salt	552.1
1A-210	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-morpholin-4-yl-ethanone hydrochloride salt	430.2
1A-211	1-[5-(4-chlorophenyl)-1-(2-fluoro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-morpholin-4-yl-ethanone hydrochloride salt	414.3
1A-212	2-(4-Benzoyl-piperazin-1-yl)-1-[5-(4-chlorophenyl)-1-(2-fluoro-phenyl)-4-methyl-1H-pyrazol-3-yl]-ethanone hydrochloride salt	517.3
1A-213	1-[5-(4-chlorophenyl)-1-(2-fluoro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-(4-fluoro-benzoyl)-piperazin-1-yl]-ethanone hydrochloride salt	535.3
1A-214	1-[5-(4-chlorophenyl)-1-(2-fluoro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-piperidin-1-yl-ethanone hydrochloride salt	486.3
1A-215	1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-ethanone hydrochloride salt	487.0
1A-216	N-(1-{2-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-piperidin-4-yl)-2,2,2-trifluoro-acetamide hydrochloride salt	539.1

Example 2 illustrates the preparation of compounds of Formula (I) where L is $-CR^4(OR^5)-$, where R^4 and R^5 are both hydrogen.

Example 2

2-(Benzyl-isopropyl-amino)-1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-ethanol (2A-1):

To the solution of 2-(benzyl-isopropyl-amino)-1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-ethanone hydrochloride 1A-1(250 mg, 0.47 mmol) in 2 ml ethanol was added sodium borohydride (32 mg, 0.71 mmol). The reaction was monitored by TLC (30% ethyl acetate/hexanes). After the completion, the reaction was quenched with water and partitioned

between ethyl acetate and saturated $NaHCO_3$. The organic layer was washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. The product was further purified by chromatography (silica gel, 40% ethyl acetate/hexanes) to give the title compound 2A-1(187 mg).

^1H NMR in CD_2Cl_2 (ppm): δ 7.4-7.1 (m, 13H), 4.71 (d, 1H), 3.9-3.57 (AB quartet, 2H), 3.04 (m, 1H), 2.90-2.77 (AB quartet, 2H), 2.00 (s, 3H), 1.15 (d, 3H), 1.05 (d, 3H).

ms (LCMS) m/z = 494.2 (M+1)

The compounds listed in Table 2 below were prepared using the general procedures described above and the appropriate α-aminoketone compound from Example 1.

Table 2

Example No.	Compound Name	LCMS m/z (M + 1)
2A-2	2-(Benzyl-isopropyl-amino)-1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-ethanol hydrochloride salt	494.2
2A-3	2-[Benzyl-(2-hydroxy-ethyl)-amino]-1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-ethanol	496.1
2A-4	1-Benzylamino-1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-ethanol hydrochloride salt	452.1
2A-5	1-[5-(4-Chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(2,6-dimethyl-morpholin-4-yl)-ethanol	460.2
2A-6	1-[5-(4-Chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-(3-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-ethanol	576.1
2A-7	1-[5-(4-Chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-(5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-ethanol	576.0
2A-8	1-{2-[1-(2-Chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-hydroxy-ethyl}-4-phenyl-piperidine-4-carbonitrile	531.1

Example No.	Compound Name	LCMS m/z (M + 1)
2A-9	1-[1-(2-Chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-(1-hydroxy-ethyl)-4-phenyl-piperidin-1-yl]-ethanol	550.1
2A-10	1-[5-(4-Chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(3,3-dimethyl-piperidin-1-yl)-ethanol	458.1
2A-11	1-[1-(2-Chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(2-methoxymethyl-pyrrolidin-1-yl)-ethanol	460.1
2A-12	1-[1-(2-Chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl)-ethanol	444.1
2A-13	1-[1-(2-Chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(ethyl-[1,3,4]thiadiazol-2-yl-amino)-ethanol	474.0
2A-14	1-[5-(4-Chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[3-(3-methoxy-phenyl)-piperidin-1-yl]-ethanol	536.8
2A-14	1-{2-[1-(2-Chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-hydroxy-ethyl}-3-o-tolyl-pyrrolidin-3-ol	522.8
2A-15	1-[5-(4-Chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-(4-methyl-4H-[1,2,4]triazol-3-yl)-piperidin-1-yl]-ethanol	511.8
2A-16	1-[5-(4-Chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]- 2-[4-(3,4-dihydro-1H-isoquinolin-2-yl)-piperidin-1-yl]- ethanol	561.1
2A-17	1-{2-[1-(2-Chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-hydroxy-ethyl}-4-phenyl-decahydroquinolin-4-ol	576.9
2A-18	1-[5-(4-Chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(4-trifluoromethyl-10-aza-tricyclo[6.3.1.0]dodeca-2,4,6-trien-10-yl)-ethanol	572.8
2A-19	1-[1-(2-Chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(3-phenyl-piperidin-1-yl)-ethanol	506.8
2A-20	N-(1-{2-[1-(2-Chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-hydroxy-ethyl}-pyrrolidin-3-yl)-N-methyl-acetamide	486.9
2A-21	1-[5-(4-Chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]- 2-(2,3-dihydro-5H-benzo[f][1,4]oxazepin-4-yl)-ethanol	494.8

Example No.	Compound Name	LCMS m/z (M + 1)
2A-22	1-[5-(4-Chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[methyl-(1-methyl-1H-pyrazol-4-ylmethyl)-amino]-ethanol	470.1
2A-23	α-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-spiro[isobenzofuran-1(3H),4'piperidine]-1'-ethanol	534.8
2A-24	1-[1-(2-Chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(methyl-pyridin-2-ylmethyl-amino)-ethanol	467.7
2A-24	1-[1-(2-Chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[3-(3-methoxy-phenyl)-3-propyl-pyrrolidin-1-yl]-ethanol	564.9
2A-25	1-{2-[1-(2-Chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-hydroxy-ethyl}-4-phenyl-piperidine-4-carbonitrile hydrochloride salt	530.9
2A-26	1-[5-(4-Chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(3,3-dimethyl-piperidin-1-yl)-ethanol hydrochloride salt	458.1
2A-27	1-[5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(3,3-dimethyl-piperidin-1-yl)-ethanol	492.1
2A-28	1-{2-[5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-hydroxy-ethyl}-4-phenyl-piperidine-4-carbonitrile	565.1
2A-29	1-[5-(4-Chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(3,3-dimethyl-piperidin-1-yl)-2-methyl-propan-1-ol	486.3
2A-30	1-[1-(2-Chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-isopropylamino-2-methyl-propan-1-ol	432.3
2A-31	1-{2-[5-(4-Chlorophenyl)-1-(2-fluoro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-hydroxy-ethyl}-4-phenyl-piperidine-4-carbonitrile	515.2
2A-32	1-[5-(4-Chlorophenyl)-1-(2-fluoro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-(3,3-dimethyl-piperidin-1-yl)-ethanol	442.3
2A-33	1-{2-[1-(2-Chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-hydroxy-1,1-dimethyl-ethyl}-4-phenyl-piperidine-4-carbonitrile	559.3
2A-34	(4-{2-[5-(4-Chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-hydroxy-ethyl}-piperazin-1-yl)-phenyl-methanone	535.9

Example No.	Compound Name	LCMS m/z (M + 1)
2A-35	(4-{2-[5-(4-Chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-hydroxy-ethyl}-piperazin-1-yl)-furan-2-yl-methanone	525.9
2A-36	2-(Benzyl-bicyclo[2.2.1]hept-2-yl-amino)-1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-ethanol	547.0
2A-37	1-[5-(4-Chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(3,5-dimethyl-piperidin-1-yl)-ethanol	458.9
2A-38	1-[5-(4-Chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(4-phenyl-piperidin-1-yl)-ethanol	506.2
2A-39	4-{2-[5-(4-Chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-hydroxy-ethyl}-piperazine-1-carboxylic acid 2-hydroxy-2-methyl-propyl ester	547.9
2A-40	1-[5-(4-Chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-(tetrahydro-furan-2-ylmethyl)-piperazin-1-yl]-ethanol	515.9
2A-41	3-{2-[1-(2-Chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-hydroxy-ethyl}-2,3,4,4a-tetrahydro-1H-3,9a-diaza-fluoren-9-one	533.9
2A-42	2-[(1-Benzyl-pyrrolidin-3-ylmethyl)-methyl-amino]-1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-ethanol	551.6
2A-43	2-(3-Benzylamino-8-aza-bicyclo[3.2.1]oct-8-yl)-1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-ethanol	563.6
2A-44	1-[1-(2-Chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(1-p-tolyl-3-aza-bicyclo[3.1.0]hex-3-yl)-ethanol	518.9
2A-45	1-[1-(2-Chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethanol	508.9
2A-46	2-[Benzyl-(2-hydroxymethyl-cyclohexyl)-amino]-1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-ethanol	565.0
2A-47	1-[5-(4-Chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(3-hydroxymethyl-3,4-dihydro-1H-isoquinolin-2-yl)-ethanol	508.9
2A-48	3-[{2-[5-(4-Chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-hydroxy-ethyl}-(2,6-dichloro-benzyl)-amino]-propan-1-ol	579.2

Example No.	Compound Name	LCMS m/z (M + 1)
2A-49	2-(Benzyl-{2-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-hydroxy-ethyl}-amino)-cyclobutanol	522.9
2A-50	α-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-3,4-dihydro-6-methoxy-spiro[naphthalene-1(2H),4'piperidine]-1'-ethanol	577.0
2A-51	(1-{2-[5-(4-Chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-hydroxy-ethyl}-piperidin-3-yl)-pyrrolidin-1-yl-methanone	527.9
2A-52	1-[5-(4-Chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(3-methyl-3-phenyl-piperidin-1-yl)-ethanol	521.2
2A-53	(4-{2-[5-(4-Chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-hydroxy-ethyl}-piperazin-1-yl)-pyridin-4-yl-methanone	538.6
2A-54	6-(4-{2-[5-(4-Chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-hydroxy-ethyl}-piperazin-1-yl)-nicotinonitrile	534.2
2A-55	1-{2-[1-(2-Chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-hydroxy-ethyl}-4-cyclohexylamino-piperidine-4-carboxylic acid amide	572.6
2A-56	1-{2-[1-(2-Chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-hydroxy-ethyl}-4-isopropylamino-piperidine-4-carboxylic acid amide	531.2
2A-57	1-[5-(4-Chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(4-pyrimidin-2-yl-piperazin-1-yl)-ethanol	507.9
2A-58	1-[1-(2-Chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-(methyl-pyridin-4-ylmethyl-amino)-ethanol	468.0
2A-59	1-[5-(4-Chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-(5-chloro-pyridin-2-yl)-piperazin-1-yl]-ethanol	543.1
2A-60	1-[1-(2-Chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-[(1,1-dioxo-tetrahydro-1&-thiophen-3-yl)-methyl-amino]-ethanol	494.8
2A-61	2-({2-[1-(2-Chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-hydroxy-ethyl}-methyl-amino)-1-phenyl-propan-1-ol	510.9
2A-62	1-{2-[5-(4-Chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-hydroxy-ethyl}-piperidin-3-ol	446.8

Example No.	Compound Name	LCMS m/z (M + 1)
2A-63	1-[5-(4-Chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-piperidin-1-yl-ethanol hydrochloride salt	430.3

Example 3 illustrates the preparation of ether derivatives (i.e., L = -$CR^4(OR^5)$-) from the corresponding alcohol (L = -$CR^4(OH)$-) from Example 2.

Example 3

Benzyl-{2-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-2-methoxy-ethyl}-isopropyl-amine(3A-1):

To the solution of 2-(benzyl-isopropyl-amino)-1-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-ethanol 2A-1 (50 mg, 0.1 mmol) in 0.2 ml DMF was added sodium hydride (5 mg, 0.125 mmol, 60% w/w). After it was stirred for 1 hour, the reaction mixture was cooled to 0°C. Methyl iodide (15 mg, 0.11 mmol) was added and the reaction mixture was then warmed up to room temperature. Stirring was continued for another 2 hours. The reaction mixture was partitioned with ethyl acetate and water. The organic layer was washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by chromatography (silica gel, 30% ethyl acetate/hexanes) to give the title compound 3A-1 as a white waxy solid (27 mg).

^{1}H NMR in CD_2Cl_2 (ppm): δ7.4-7.05 (m, 13H); 4.42 (t, 1H); 3.40-3.56 (AB quartet, 2H); 3.26 (s, 3H); 3.01-2.87 (m, 3H); 1.99 (s, 3H); 1.00 (d, 3H); 0.96 (d, 3H);

ms (LCMS) m/z = 508.2 (M+1)

Example 4 illustrates the conversion of an α-aminoketone of the present invention (L = -C(O)-) to its corresponding alcohol having a R^4 group other than hydrogen (i.e., L = -$CR^4(OH)$-).

Example 4

1-(Benzyl-isopropyl-amino)-2-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-propan-2-ol (4A-1):

Methyl magnesium bromide (0.1 ml, 0.144 mmol) was added dropwise into the solution of 2-(benzyl-isopropyl-amino)-1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-ethanone (61 mg, 0.12 mmol) in 0.5 ml THF at room temperature. After 2 h, the reaction mixture was then partitioned with ethyl acetate and saturated NH_4Cl. The organic layer was washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by chromatography (silica gel, 30% ethyl acetate/hexanes) to give the title compound 4A-1 as a white waxy solid (24 mg).

^1H NMR in CD_2Cl_2 (ppm): δ7.4-6.95 (m, 13H), 3.75-3.55 (AB quartet, 2H); 3.23-2.65 (AB quartet, 2H); 2.90 (m, 1H); 2.16 (s, 3H); 1.50 (s, 3H); 1.05 (d, 3H); 0.98 (d, 3H);

ms (LCMS) m/z = 508.2 (M+1)

Example 5 illustrates the preparation of compounds of the present invention where L is $-CR^4(OR^5)-$, where R^5 and either R^8 or R^9 form an ethylene bridge.

Example 5

4-Benzyl-2-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-morpholine (5A-1):

The suspension of 2-[benzyl-(2-hydroxy-ethyl)-amino]-1-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-ethanol 2A-3 (150 mg, 0.3 mmol) in 48% hydrobromic acid (0.3 ml) was heated to 100 °C for 2 hours. After the reaction was complete, the reaction mixture was cooled to room temperature and partitioned with ethyl acetate and saturated $NaHCO_3$. The organic layer was washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by chromatography (silica gel, 40% ethyl acetate/hexanes) to give the title compound 5A-1 (77 mg).

^{1}H NMR in CD_2Cl_2 (ppm): δ7.42-7.13 (m, 3H); 4.76 (d, 1H); 3.98 (d, 1H); 3.82 (t, 1H); 3.60 (s, 2H); 2.97 (d, 1H); 2.80 (d, 1H); 2.54 (t, 1H); 2.32 (t, 1H); 2.10 (s, 3H);

ms (LCMS) m/z = 478.1 (M+1)

2-[1-(2-Chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-morpholine hydrochloride (5A-2):

The solution of 4-benzyl-2-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-morpholine 5A-1 (840 mg, 1.7 mmol), 1-chloroethyl chloroformate (0.2 ml, 1.87 mmol), and 1, 8-bis(dimethylamino)naphthalene (72 mg, 0.34 mmol) in 5 ml 1,2-dichloroethane was heated to 50 °C for 3 hours. The reaction mixture was then cooled to room temperature and concentrated in *vacuo*. The residue was dissolved in 5 ml MeOH and heated to reflux for 2 hours. After the reaction was completed, the reaction mixture was cooled to room temperature and concentrated. The residue was stirred in 5 ml diethyl ether and the product was precipitated and collected by filtration to give the title compound 5A-2 as a white solid (525 mg).

^{1}H NMR in CD_3OD (ppm): δ7.45-7.36 (m, 4H); 7.30 (d, 2H); 7.15 (d, 2H); 4.71 (d, 1H); 3.95 (d, 1H); 3.78 (t, 1H); 3/20-2.82 (m, 4H);

ms (LCMS) m/z = 388.1 (M+1)

2-[5-(4-Chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]- 4-cyclohexyl-morpholine (5A-3):

Triethyl amine (37 μl, 0.27 mmol) was added into the solution of 2-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-morpholine hydrochloride 5A-2 (75 mg, 0.18 mmol) and cyclohexanone (18 μl, 0.18 mmol) in 0.5 ml 1,2-dichloroethane. The reaction mixture was then treated with sodium triacetoxyborohydride (52 mg, 0.25 mmol) followed by acetic acid at room temperature. Upon the completion of the reaction, the reaction mixture was partitioned with ethyl acetate and saturated $NaHCO_3$. The organic layer was washed with brine, dried over sodium sulfate, and

concentrated *in vacuo*. The residue was purified by chromatography (silica, 60% ethyl acetate/hexanes) to give the title compound 5A-3 as a white solid (40 mg).

^{1}H NMR in CD_3OD (ppm): δ7.43-7.38 (m, 4H); 7.30 (d, 2H); 7.17 (d, 2H); 4.00 (d, 1H); 3.80 (t, 1H); 3.05 (d, 1H); 2.84 (d, 1H); 2.72 (t, 1H); 2.54 (t, 1H); 2.35 (m, 1H); 2.13 (s, 3H); 2.00-1.25 (m, 10H);

ms (LCMS) m/z = 470.1 (M+1)

The compounds listed in Table 3 below were prepared using the general procedures described above for the preparation of compounds 5A-1, 5A-2 and 5A-3.

Table 3

Example No.	Compound Name	LCMS m/z (M + 1)
5A-4	2-[1-(2-Chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-4-isopropyl-morpholine	430.1
5A-5	2-[5-(4-Chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-4-(tetrahydro-pyran-4-yl)-morpholine	471.9
5A-6	2-[1-(2-Chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-4-(6-methyl-pyridin-2-ylmethyl)-morpholine	493.3
5A-7	2-[1-(2-Chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-4-(4-trifluoromethyl-benzyl)-morpholine	546.3
5A-8	4-{2-[1-(2-Chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-morpholin-4-ylmethyl}-quinoline	529.2
5A-9	5-Chloro-2-{2-[5-(4-chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-morpholin-4-ylmethyl}-1H-indole	553.2
5A-10	2-[1-(2-Chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-4-(5-methyl-2-phenyl-oxazol-4-ylmethyl)-morpholine hydrochloride salt	559.5

Example 6 illustrates compounds of the present invention where either R^8 or R^9 is an acyl group or sulfonate group.

Example 6

2-[5-(4-Chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-4-(propane-2-sulfonyl)-morpholine (6A-1):

To a stirred suspension of 2-[1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]- morpholine hydrochloride 5A-2 (75 mg, 0.18 mmol) and triethylamine (49 μL, 0.36 mmol) in dichloromethane (0.5 ml) was added isopropylsulfonyl chloride (0.22 μL 0.2 mmol) dropwise. After stirring for 18 h, the reaction was partitioned between ethyl acetate and saturated sodium bicarbonate. The organic layer was washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by chromatography (silica, 40-50% ethyl acetate/hexanes) to give the title compound 6A-1 as a colorless foam (49 mg).

^{1}H NMR in CD_3OD (ppm): δ7.43-7.38 (m, 4H); 7.30 (d, 2H); 7.15 (d, 2H); 4.70 (d, 1H); 4.05 (d, 1H); 3.84-3.17 (m, 6H); 2.15 (s, 3H); 1.36 (d, 6H).

ms (LCMS) m/z = 494.1 (M+1).

The compounds listed below in Table 4 were prepared using the general procedures described above with the appropriate acid halide or sulfonyl halide.

Table 4

Example No.	Compound Name	LCMS m/z (M + 1)
6A-2	2-[5-(4-Chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-4-(toluene-4-sulfonyl)-morpholine	542.1
6A-3	{2-[5-(4-Chlorophenyl)-1-(2-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-morpholin-4-yl}-phenyl-methanone	492.1
6A-4	1-{2-[1-(2-Chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazol-3-yl]-morpholin-4-yl}-2-methyl-propan-1-one	458.1

Example 7 illustrates the preparation of the imidazole derivatives as outlined in Scheme IV above.

Example 7

Preparation of 2,4-dichloro-N-(4-chloro-phenyl)-benzamidine (I-7a):

Trimethylaluminum (2M in toluene, 111.3 ml, 222.6 mmol) was added dropwise to a solution of 4-chloro-phenylamine (20 g, 156.8 mmol) in toluene (700 ml) at 0 °C over a 70 minute period under N_2. The reaction mixture was warmed to room temperature and stirred for 3.5 hours. A solution of benzonitrile (32.4 g, 188.1 mmol) in toluene (100 ml) was added and the reaction mixture was heated to 85°C overnight, during which time it became homogeneous. The reaction mixture was then cooled to room temperature and poured over a slurry of silica gel in chloroform/methanol (2:1). After filtration, the residue was washed with a mixture of methylene chloride/methanol (2:1). The combined filtrates were concentrated *in vacuo*, and the resulting yellow solid was triturated with hexanes/ether (2:1). The yellowish solid 2,4-dichloro-N-(4-chloro-phenyl)-benzamidine I-7a (34.15g, 73%) was used in the next reaction without further purification.

Preparation of 1-(4-Chloro-phenyl)-2-(2,4-dichloro-phenyl)-4-hydroxy-4,5-dihydro-1H-imidazole-4-carboxylic acid ethyl ester (I-7b):

A mixture of 2,4-dichloro-N-(4-chloro-phenyl)-benzamidine I-7a (34 g, 113.5 mmol) and sodium bicarbonate (19.1 g, 227 mmol) in 2-propanol (600 ml) was treated with 3-bromo-2-oxo-propionic acid ethyl ester (20 ml, 158.9 mmol). The reaction mixture was heated to 85 °C overnight, and the solvent was removed *in vacuo*. The residue was partitioned between methylene chloride and water, and the layers were separated. The organic phase was dried over anhydrous magnesium sulfate and concentrated. The residue was triturated with ether /hexanes (1:3), and the yellow solid, 1-(4-chloro-phenyl)-2-(2,4-dichloro-phenyl)-4-hydroxy-4,5-dihydro-1H-imidazole-4-carboxylic acid ethyl ester I-7b (45 g, 96%), was collected by filtration.

Preparation of 1-(4-Chloro-phenyl)-2-(2,4-dichloro-phenyl)-1H-imidazole-4-carboxylic acid ethyl ester (I-7c):

A mixture of 1-(4-chloro-phenyl)-2-(2,4-dichloro-phenyl)-4-hydroxy-4,5-dihydro-1H-imidazole-4-carboxylic acid ethyl ester I-7b (45 g, 108.8 mmol) and *p*-toluenesulfonic acid monohydrate (2.1 g, 10.8 mmol) in toluene (540 ml) was heated to reflux overnight. The reaction mixture was cooled and the solvent removed *in vacuo*. The crude residue was taken up in methylene chloride and washed with water, aqueous sodium bicarbonate, and brine. After drying over anhydrous magnesium sulfate and concentrating, the residue was purified by plug filtration on 600 g silica gel using ethyl acetate/hexanes (20:80) to give pure 1-(4-chloro-phenyl)-2-(2,4-dichloro-phenyl)-1H-imidazole-4-carboxylic acid ethyl ester I-7c (30 g, 69.7%).

Preparation of 1-(4-Chloro-phenyl)-2-(2,4-dichloro-phenyl)-1H-imidazole-4-carboxylic acid (I-7d):

A solution of LiOH (6.36 g, 152 mmol) was added to a suspension of 1-(4-chloro-phenyl)-2-(2,4-dichloro-phenyl)-1H-imidazole-4-carboxylic acid ethyl ester I-7c (30 g, 75.8 mmol) in methanol (380 ml). The reaction mixture was heated to reflux for 1h and then cooled to room temperature. Most of the solvent was removed *in vacuo*, and the residue was diluted with water and acidified with 3N HCl. The red-brown precipitate was collected by filtration and triturated with 100 ml ethyl acetate/hexanes (20:80) to afford 1-(4-chloro-phenyl)-2-(2,4-dichloro-phenyl)-1H-imidazole-4-carboxylic acid I-7d (26.3 g, 94%) as a pale yellow solid.

Preparation of 1-(4-Chloro-phenyl)-2-(2,4-dichloro-phenyl)-1H-imidazole-4-carboxylic acid methoxy-methyl-amide (I-7e):

To a solution of 1-(4-chloro-phenyl)-2-(2,4-dichloro-phenyl)-1H-imidazole-4-carboxylic acid I-7d (1.31 g, 3.57 mmol) and N,O-dimethylhydroxylamine hydrochloride (0.42 g, 1.2 equiv) in THF (14 ml) were added TEA (4.97 ml, 10 equiv) and 1-propane phosphonic acid cyclic anhydride (3.21 ml, 1.5 equiv). The reaction mixture was stirred at room

temperature overnight, diluted with ethyl acetate and washed with water, 10% citric acid, and saturated aqueous sodium chloride. The organic phase was dried over anhydrous magnesium sulfate and concentrated to a foam which was purified by flash column chromatography (silica, 70:30 ethyl acetate/hexane grading to ethyl acetate) to give 1-(4-chloro-phenyl)-2-(2,4-dichloro-phenyl)-1H-imidazole-4-carboxylic acid methoxy-methyl-amide I-7e (485 mg, 33%).

Preparation of 1-[1-(4-Chloro-phenyl)-2-(2,4-dichloro-phenyl)-1H-imidazol-4-yl]-ethanone (I-7f):

A solution of 1-(4-chloro-phenyl)-2-(2,4-dichloro-phenyl)-1H-imidazole-4-carboxylic acid methoxy-methyl-amide I-7e (1.64 g, 3.99 mmol) in THF (16 ml) was cooled to 0 °C, and methylmagnesium iodide (4.4 ml of a 3.0 M solution in Et_2O, 9.9 mmol) was added dropwise *via* syringe. The resultant solution was stirred at 0 °C for 1 h, and then the reaction mixture was poured into cold 1N HCl (100 ml). The mixture was extracted with ethyl acetate (2 85-ml portions), and the combined extracts were washed with saturated aqueous sodium chloride (100 ml). The organics were dried over anhydrous magnesium sulfate and were concentrated to afford 1-[1-(4-chloro-phenyl)-2-(2,4-dichloro-phenyl)-1H-imidazol-4-yl]-ethanone I-7f (1.41 g, 97%) that was used in the next reaction without any further purification.

Preparation of 2-Bromo-1-[1-(4-chloro-phenyl)-2-(2,4-dichloro-phenyl)-1H-imidazol-4-yl]-ethanone (I-7g):

Aqueous HBr (0.98 ml of a 48% solution) was added to a solution of 1-[1-(4-chloro-phenyl)-2-(2,4-dichloro-phenyl)-1H-imidazol-4-yl]-ethanone I-7f (1.60 g, 4.38 mmol) in acetic acid (20 ml). Bromine (0.226 ml, 4.38 mmol) was added next to the reaction mixture in a dropwise manner. The resultant orange solution was stirred at 23 °C for 1 h before warming to 40 °C for 40 min and then cooling to 23 °C for 60 h. The reaction mixture was poured into a mixture of ice and saturated aqueous sodium bicarbonate, and the

resultant mixture was extracted with ethyl acetate (2 200-ml portions). The combined organics were washed with saturated aqueous sodium bicarbonate (100 ml) and were dried over anhydrous magnesium sulfate and concentrated to afford 2-bromo-1-[1-(4-chloro-phenyl)-2-(2,4-dichloro-phenyl)-1H-imidazol-4-yl]-ethanone I-7g (1.03 g, 53%).

Preparation of 1-[1-(4-Chloro-phenyl)-2-(2,4-dichloro-phenyl)-1H-imidazol-4-yl]-2-morpholin-4-yl-ethanone (7A-1):

Morpholine (0.04 ml, 0.426 mmol) was added to a solution of 2-bromo-1-[1-(4-chloro-phenyl)-2-(2,4-dichloro-phenyl)-1H-imidazol-4-yl]-ethanone I-7g (63 mg, 0.142 mmol) in THF (3 ml). The resultant solution was stirred at 23 °C for 12 hours, diluted with 50 ml methyl *tert*-butyl ether, and washed with 25 ml water. The organic phase was dried over anhydrous magnesium sulfate and concentrated. The residue was co-evaporated with hexanes once to afford 1-[1-(4-chloro-phenyl)-2-(2,4-dichloro-phenyl)-1H-imidazol-4-yl]-2-morpholin-4-yl-ethanone 7A-1 (52 mg, 81%) as a solid.

ms (LCMS) m/z = 450.2 (M+1). ^{1}H NMR in CD_3OD (ppm): δ8.3 (s, 1H); 7.56 (d, 1H); 7.50 (d, 2H); 4.72 (m, 3H); 7.24 (d, 1H); 3.89 (s, 2H); 3.74 (t, 4H); 2.64 (m, 4H).

The compounds listed below in Table 5 were prepared using the general procedures described above for the preparation of Example 7A-1.

Table 5

Example No.	Compound Name	LCMS m/z (M + 1)
7A-2	1-[1-(4-Chloro-phenyl)-2-(2,4-dichloro-phenyl)-1H-imidazol-4-yl]-2-(4-ethyl-piperazin-1-yl)-ethanone	477.3
7A-3	1-[1-(4-Chloro-phenyl)-2-(2,4-dichloro-phenyl)-1H-imidazol-4-yl]-2-piperidin-1-yl-ethanone	448.3
7A-4	1-[1-(4-Chloro-phenyl)-2-(2,4-dichloro-phenyl)-1H-imidazol-4-yl]-2-pyrrolidin-1-yl-ethanone	434.2

Example No.	Compound Name	LCMS m/z (M + 1)
7A-5	1-[1-(4-Chloro-phenyl)-2-(2,4-dichloro-phenyl)-5-methyl-1H-imidazol-4-yl]-2-piperidin-1-yl-ethanone	464.5
7A-6	1-[1-(4-Chloro-phenyl)-2-(2,4-dichloro-phenyl)-5-methyl-1H-imidazol-4-yl]-2-morpholin-4-yl-ethanone	464.5

PHARMACOLOGICAL TESTING

The utility of the compounds of the present invention in the practice of the instant invention can be evidenced by activity in at least one of the protocols described hereinbelow. The following acronyms are used in the protocols described below.

BSA - bovine serum albumin

DMSO - dimethylsulfoxide

EDTA - ethylenediamine tetracetic acid

PBS – phosphate-buffered saline

EGTA - ethylene glycol-*bis*(β-aminoethyl ether) N,N,N',N'-tetraacetic acid

GDP - guanosine diphosphate

sc - subcutaneous

po - orally

ip - intraperitoneal

icv - intra cerebro ventricular

iv - intravenous

[^{3}H]SR141716A - radiolabeled N-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide hydrochloride available from Amersham Biosciences, Piscataway, NJ.

[^{3}H] 5-(1,1-dimethyl-heptyl)-2-[5-hydroxy-2-(3-hydroxy-propyl)-cyclohexyl]-phenol available from NEN Life Science Products, Boston, MA.

AM251 - *N* -(piperidin-1-yl)-1-(2,4-dichlorophenyl)-5-(4-iodophenyl)-4-methyl-1H-pyrazole-3-carboxamide available from Tocris™, Ellisville, MO.

All of the compounds listed in the Example section above were tested in the CB-1 receptor binding assay below. Those compounds having an activity <20 nM were then tested in the CB-1 GTPγ [^{35}S] Binding Assay and the CB-2 binding assay described below in the Biological Binding Assays section. Selected compounds were then tested *in vivo* using one or more of the functional assays described in the Biological Functional Assays section below.

In Vitro Biological Assays

Bioassay systems for determining the CB-1 and CB-2 binding properties and pharmacological activity of cannabinoid receptor ligands are described by Roger G. Pertwee in "Pharmacology of Cannabinoid Receptor Ligands" Current Medicinal Chemistry, **6**, 635-664 (1999) and in WO 92/02640 (U.S. Application No. 07/564,075 filed August 8, 1990, incorporated herein by reference).

The following assays were designed to detect compounds that inhibit the binding of [^{3}H] SR141716A (selective radiolabeled CB-1 ligand) and [^{3}H] 5-(1,1-dimethylheptyl)-2-[5-hydroxy-2-(3-hydroxypropyl)-cyclohexyl]-phenol; radiolabeled CB-1/CB-2 ligand) to their respective receptors.

Rat CB-1 Receptor Binding Protocol

PelFreeze brains (available from Pel Freeze Biologicals, Rogers, Arkansas) were cut up and placed in tissue preparation buffer (5 mM Tris HCl, pH = 7.4 and 2 mM EDTA), polytroned at high speed and kept on ice for 15 minutes. The homogenate was then spun at 1,000 X g for 5 minutes at 4°C. The supernatant was recovered and centrifuged at 100,000 X G for 1 hour at 4°C. The pellet was then re-suspended in 25 ml of TME (25 nM Tris, pH = 7.4, 5 mM $MgCl_2$, and 1 mM EDTA) per brain used. A protein

assay was performed and 200 µl of tissue totaling 20 µg was added to the assay.

The test compounds were diluted in drug buffer (0.5% BSA, 10% DMSO and TME) and then 25 µl were added to a deep well polypropylene plate. [^{3}H] SR141716A was diluted in a ligand buffer (0.5% BSA plus TME) and 25 µl were added to the plate. A BCA protein assay was used to determine the appropriate tissue concentration and then 200 µl of rat brain tissue at the appropriate concentration was added to the plate. The plates were covered and placed in an incubator at 20°C for 60 minutes. At the end of the incubation period 250 µl of stop buffer (5% BSA plus TME) was added to the reaction plate. The plates were then harvested by Skatron onto GF/B filtermats presoaked in BSA (5 mg/ml) plus TME. Each filter was washed twice. The filters were dried overnight. In the morning the filters were counted on a Wallac Betaplate™ counter (available from PerkinElmer Life Sciences™, Boston, MA).

Human CB-1 Receptor Binding Protocol

Human embryonic kidney 293 (HEK 293) cells transfected with the CB-1 receptor cDNA (obtained from Dr. Debra Kendall, University of Connecticut) were harvested in homogenization buffer (10 mM EDTA, 10 mM EGTA, 10 mM Na Bicarbonate, protease inhibitors; pH = 7.4), and homogenized with a Dounce Homogenizer. The homogenate was then spun at 1,000X g for 5 minutes at 4°C. The supernatant was recovered and centrifuged at 25,000X G for 20 minutes at 4°C. The pellet was then re-suspended in 10 ml of homogenization buffer and re-spun at 25,000X G for 20 minutes at 4°C. The final pellet was re-suspended in 1ml of TME (25 mM Tris buffer (pH = 7.4) containing 5 mM $MgCl_2$ and 1 mM EDTA). A protein assay was performed and 200 µl of tissue totaling 20 µg was added to the assay.

The test compounds were diluted in drug buffer (0.5% BSA, 10% DMSO and TME) and then 25 µl were added to a deep well polypropylene plate. [^{3}H] SR141716A was diluted in a ligand buffer (0.5% BSA plus TME)

and 25 µl were added to the plate. The plates were covered and placed in an incubator at 30°C for 60 minutes. At the end of the incubation period 250 µl of stop buffer (5% BSA plus TME) was added to the reaction plate. The plates were then harvested by Skatron onto GF/B filtermats presoaked in BSA (5 mg/ml) plus TME. Each filter was washed twice. The filters were dried overnight. In the morning the filters were counted on a Wallac Betaplate™ counter (available from PerkinElmer Life Sciences™, Boston, MA).

An activity range from 0.1 to 100 nanomolar was observed for the compounds listed in Examples 1 through 7. As a specific example, a binding affinity of 79 nanomolar was observed for the compound of Example 5A-6. Example 5A-6 was chosen for illustrative purposes only and does not imply that the compound of Example 5A-6 is a preferred compound.

CB-2 Receptor Binding Protocol

Chinese hamster ovary-K1 (CHO-K1) cells transfected with CB-2 cDNA (obtained from Dr. Debra Kendall, University of Connecticut) were harvested in tissue preparation buffer (5 mM Tris-HCl buffer (pH = 7.4) containing 2 mM EDTA), polytroned at high speed and kept on ice for 15 minutes. The homogenate was then spun at 1,000X g for 5 minutes at 4°C. The supernatant was recovered and centrifuged at 100,000X G for 1 hour at 4°C. The pellet was then re-suspended in 25 ml of TME (25 mM Tris buffer (pH = 7.4) containing 5 mM $MgCl_2$ and 1 mM EDTA) per brain used. A protein assay was performed and 200 µl of tissue totaling 10 µg was added to the assay.

The test compounds were diluted in drug buffer (0.5% BSA, 10% DMSO, and 80.5% TME) and then 25 µl were added to the deep well polypropylene plate. [^{3}H] 5-(1,1-Dimethyl-heptyl)-2-[5-hydroxy-2-(3-hydroxy-propyl)-cyclohexyl]-phenol was diluted a ligand buffer (0.5% BSA and 99.5% TME) and then 25 µl were added to each well at a concentration of 1 nM. A BCA protein assay was used to determine the appropriate tissue

concentration and 200 μl of the tissue at the appropriate concentration was added to the plate. The plates were covered and placed in an incubator at 30°C for 60 minutes. At the end of the incubation period 250 μl of stop buffer (5% BSA plus TME) was added to the reaction plate. The plates were then harvested by Skatron format onto GF/B filtermats presoaked in BSA (5 mg/ml) plus TME. Each filter was washed twice. The filters were dried overnight. The filters were then counted on the Wallac Betaplate™ counter.

CB-1 GTPγ [^{35}S] Binding Assay

Membranes were prepared from CHO-K1 cells stably transfected with the human CB-1 receptor cDNA. Membranes were prepared from cells as described by Bass et al, in "Identification and characterization of novel somatostatin antagonists," Molecular Pharmacology, **50**, 709-715 (1996). GTPγ [^{35}S] binding assays were performed in a 96 well FlashPlate™ format in duplicate using 100 pM GTPγ[^{35}S] and 10 μg membrane per well in assay buffer composed of 50 mM Tris HCl, pH 7.4, 3 mM $MgCl_2$, pH 7.4, 10 mM $MgCl_2$, 20 mM EGTA, 100 mM NaCl, 30 μM GDP, 0.1 % bovine serum albumin and the following protease inhibitors: 100 μg/ml bacitracin, 100 μg/ml benzamidine, 5 μg/ml aprotinin, 5 μg/ml leupeptin. The assay mix was then incubated with increasing concentrations of antagonist (10^{-10} M to 10^{-5} M) for 10 minutes and challenged with the cannabinoid agonist 5-(1,1-dimethyl-heptyl)-2-[5-hydroxy-2-(3-hydroxy-propyl)-cyclohexyl]-phenol (10 μM). Assays were performed at 30^{0}C for one hour. The FlashPlates™ were then centrifuged at 2000Xg for 10 minutes. Stimulation of GTPγ[^{35}S] binding was then quantified using a Wallac Microbeta.EC_{50} calculations done using Prism™ by Graphpad.

Inverse agonism was measured in the absense of agonist.

CB-1 FLIPR-based Functional Assay Protocol

CHO-K1 cells co-transfected with the human CB-1 receptor cDNA (obtained from Dr. Debra Kendall, University of Connecticut) and the

promiscuous G-protein G16 were used for this assay. Cells were plated 48 hours in advance at 12500 cells per well on collagen coated 384 well black clear assay plates. Cells were incubated for one hour with 4μM Fluo-4 AM (Molecular Probes) in DMEM (Gibco) containing 2.5 mM probenicid and pluronic acid (.04%). The plates were then washed 3 times with HEPES-buffered saline (containing probenicid; 2.5 mM) to remove excess dye. After 20 min the plates were added to the FLIPR individually and fluorescence levels was continuously monitored over an 80 s period. Compound additions were made simultaneously to all 384 wells after 20 s of baseline. Assays were performed in triplicate and 6 point concentration-response curves generated. Antagonist compounds were subsequently challenged with 3μM WIN 55,212-2 (agonist). Data were analyzed using Graph Pad Prism.

Detection of Inverse Agonists

The following cyclic-AMP assay protocol using intact cells was used to determine inverse agonist activity.

Cells were plated into a 96-well plate at a plating density of 10,000-14,000 cells per well at a concentration of 100 μl per well. The plates were incubated for 24 hours in a 37°C incubator. The media was removed and media lacking serum (100 μl) was added. The plates were then incubated for 18 hours at 37°C.

Serum free medium containing 1 mM IBMX was added to each well followed by 10 μl of test compound (1:10 stock solution (25 mM compound in DMSO) into 50% DMSO/PBS) diluted 10X in PBS with 0.1% BSA. After incubating for 20 minutes at 37°C, 2 μM of Forskolin was added and then incubated for an additional 20 minutes at 37°C. The media was removed, 100 μl of 0.01N HCl was added and then incubated for 20 minutes at room temperature. Cell lysate (75 μl) along with 25 μl of assay buffer (supplied in FlashPlate™ cAMP assay kit available from NEN Life Science Products Boston, MA) into a Flashplate. cAMP standards and cAMP tracer were added following the kit's protocol. The flashplate was then incubated for 18

hours at 4°C. The content of the wells were aspirated and counted in a Scintillation counter.

In Vivo Biological Assays

Cannabinoid agoinists such as Δ^9-tetrahydrocannabinol (Δ^9-THC) and 5-(1,1-dimethyl-heptyl)-2-[5-hydroxy-2-(3-hydroxy-propyl)-cyclohexyl]-phenol have been shown to affect four characteristic behaviors in mice, collectively known as the Tetrad. For a description of these behaviors see: Smith, P.B., et al. in "The pharmacological activity of anandamide, a putative endogenous cannabinoid, in mice." J. Pharmacol. Exp. Ther., **270**(1), 219-227 (1994) and Wiley, J., et al. in "Discriminative stimulus effects of anandamide in rats," Eur. J. Pharmacol., **276**(1-2), 49-54 (1995). Reversal of these activities in the Locomotor Activity, Catalepsy, Hypothermia, and Hot Plate assays described below provides a screen for *in vivo* activity of CB-1 antagonists.

All data is presented as % reversal from agonist alone using the following formula: (test compound/agonist - vehicle/agonist)/(vehicle/vehicle - vehicle/agonist). Negative numbers indicate a potentiation of the agonist activity or non-antagonist activity. Positive numbers indicate a reversal of activity for that particular test.

<u>Locomotor Activity</u>

Male ICR mice (n=6) (17-19 g, Charles River Laboratories, Inc., Wilmington, MA) were pre-treated with test compound (sc, po, ip, or icv). Fifteen minutes later, the mice were challenged with 5-(1,1-dimethyl-heptyl)-2-[5-hydroxy-2-(3-hydroxy-propyl)-cyclohexyl]-phenol (sc). Twenty-five minutes after the agonist injection, the mice were placed in clear acrylic cages (431.8 cm x 20.9 cm x 20.3 cm) containing clean wood shavings. The subjects were allowed to explore surroundings for a total of about 5 minutes and the activity was recorded by infrared motion detectors (available from Coulbourn Instruments™, Allentown, PA) that were placed on top of the

cages. The data was computer collected and expressed as "movement units."

Catalepsy

Male ICR mice (n=6)(17-19 g upon arrival) were pre-treated with test compound (sc, po, ip or icv). Fifteen minutes later, the mice were challenged with 5-(1,1-dimethyl-heptyl)-2-[5-hydroxy-2-(3-hydroxy-propyl)-cyclohexyl]-phenol (sc). Ninety minutes post injection, the mice were placed on a 6.5 cm steel ring attached to a ring stand at a height of about 12 inches. The ring was mounted in a horizontal orientation and the mouse was suspended in the gap of the ring with fore- and hind-paws gripping the perimeter. The duration that the mouse remained completely motionless (except for respiratory movements) was recorded over a 3-minute period.

The data were presented as a percent immobility rating. The rating was calculated by dividing the number of seconds the mouse remains motionless by the total time of the observation period and multiplying the result by 100. A percent reversal from the agonist was then calculated.

Hypothermia

Male ICR mice (n=5) (17-19 g upon arrival) were pretreated with test compounds (sc, po, ip or icv). Fifteen minutes later, mice were challenged with the cannabinoid agonist 5-(1,1-dimethyl-heptyl)-2-[5-hydroxy-2-(3-hydroxy-propyl)-cyclohexyl]-phenol (sc). Sixty-five minutes post agonist injection, rectal body temperatures were taken. This was done by inserting a small thermostat probe approximately 2- 2.5 cm into the rectum. Temperatures were recorded to the nearest tenth of a degree

Hot Plate

Male ICR mice (n=7) (17-19 g upon arrival) are pre-treated with test compounds (sc, po, ip or iv). Fifteen minutes later, mice were challenged with a cannabinoid agonist 5-(1,1-dimethyl-heptyl)-2-[5-hydroxy-2-(3-hydroxy-propyl)-cyclohexyl]-phenol (sc). Forty-five minutes later, each mouse was tested for reversal of analgesia using a standard hot plate meter

(Columbus Instruments). The hot plate was 10" x 10" x 0.75" with a surrounding clear acrylic wall. Latency to kick, lick or flick hindpaw or jump from the platform was recorded to the nearest tenth of a second. The timer was experimenter activated and each test had a 40 second cut off. Data were presented as a percent reversal of the agonist induced analgesia.

Food Intake

The following screen was used to evaluate the efficacy of test compounds for inhibiting food intake in Sprague-Dawley rats after an overnight fast.

Male Sprague-Dawley rats were obtained from Charles River Laboratories, Inc. (Wilmington, MA). The rats were individually housed and fed powdered chow. They were maintained on a 12 hour light/dark cycle and received food and water *ad libitum*. The animals were acclimated to the vivarium for a period of one week before testing was conducted. Testing was completed during the light portion of the cycle.

To conduct the food intake efficacy screen, rats were transferred to individual test cages without food the afternoon prior to testing, and the rats were fasted overnight. After the overnight fast, rats were dosed the following morning with vehicle or test compounds. A known antagonist was dosed (3 mg/kg) as a positive control, and a control group received vehicle alone (no compound). The test compounds were dosed at ranges between 0.1 and 100 mg/kg depending upon the compound. The standard vehicle was 0.5% (w/v) methylcellulose in water and the standard route of administration was oral. However, different vehicles and routes of administration were used to accommodate various compounds when required. Food was provided to the rats 30 minutes after dosing and the Oxymax automated food intake system (Columbus Instruments, Columbus, Ohio) was started. Individual rat food intake was recorded continuously at 10-minute intervals for a period of two hours. When required, food intake was recorded manually using an electronic scale; food was weighed every 30 minutes after food was provided

up to four hours after food was provided. Compound efficacy was determined by comparing the food intake pattern of compound-treated rats to vehicle and the standard positive control.

Alcohol Intake

The following protocol evaluates the effects of alcohol intake in alcohol preferring (P) female rats (bred at Indiana University) with an extensive drinking history. The following references provide detailed descriptions of P rats: Li ,T.-K., et al., "Indiana selection studies on alcohol related behaviors" in Development of Animal Models as Pharmacogenetic Tools (eds McClearn C. E., Deitrich R. A. and Erwin V. G.), Research Monograph 6, 171-192 (1981) NIAAA, ADAMHA, Rockville, MD; Lumeng, L, et al., "New strains of rats with alcohol preference and nonpreference" Alcohol And Aldehyde Metabolizing Systems, **3**, Academic Press, New York, 537-544 (1977); and Lumeng, L, et al., "Different sensitivities to ethanol in alcohol-preferring and -nonpreferring rats," Pharmacol, Biochem Behav., **16**, 125-130 (1982).

Female rats were given 2 hours of access to alcohol (10% v/v and water, 2-bottle choice) daily at the onset of the dark cycle. The rats were maintained on a reverse cycle to facilitate experimenter interactions. The animals were initially assigned to four groups equated for alcohol intakes: Group 1 - vehicle (n =8); Group 2 –positive control (e.g. 5.6 mg/kg AM251; n = 8); Group 3 – low dose test compound (n = 8); and Group 4 – high dose of test compound (n = 8). Test compounds were generally mixed into a vehicle of 30% (w/v) β-cyclodextrin in distilled water at a volume of 1-2 ml/kg. Vehicle injections were given to all groups for the first two days of the experiment. This was followed by 2 days of drug injections (to the appropriate groups) and a final day of vehicle injections. On the drug injection days, drugs were given sc 30 minutes prior to a 2-hour alcohol access period. Alcohol intake for all animals was measured during the test period and a comparison was made

between drug and vehicle-treated animals to determine effects of the compounds on alcohol drinking behavior.

Additional drinking studies were done utilizing female C57Bl/6 mice (Charles River). Several studies have shown that this strain of mice will readily consume alcohol with little to no manipulation required (Middaugh et al., "Ethanol Consumption by C57BL/6 Mice: Influence of Gender and Procedural Variables" Alcohol, 17 (3), 175-183, 1999; Le et al., "Alcohol Consumption by C57BL/6, BALA/c, and DBA/2 Mice in a Limited Access Paradigm" Pharmacology Biochemisrty and Behavior, 47, 375-378, 1994).

For our purposes, upon arrival (17-19 g) mice were individually housed and given unlimited access to powdered rat chow, water and a 10 % (w/v) alcohol solution. After 2-3 weeks of unlimited access, water was restricted for 20 hours and alcohol was restricted to only 2 hours access daily. This was done in a manner that the access period was the last 2 hours of the dark part of the light cycle.

Once drinking behavior stabilized, testing commenced. Mice were considered stable when the average alcohol consumption for 3 days was ± 20% of the average for all 3 days. Day 1 of test consisted of all mice receiving vehicle injection (sc or ip). Thirty to 120 minutes post injection access was given to alcohol and water. Alcohol consumption for that day was calculated (g/kg) and groups were assigned (n=7-10) so that all groups had equivocal alcohol intake. On day 2 and 3, mice were injected with vehicle or drug and the same protocol as the previous day was followed. Day 4 was wash out and no injections were given. Data was analyzed using repeated measures ANOVA. Change in water or alcohol consumption was compared back to vehicle for each day of the test. Positive results would be interpreted as a compound that was able to significantly reduce alcohol consumption while having no effect on water

Oxygen Consumption

Methods:

Whole body oxygen consumption is measured using an indirect calorimeter (Oxymax from Columbus Instruments, Columbus, OH) in male Sprague Dawley rats (if another rat strain or female rats are used, it will be specified). Rats (300-380g body weight) are placed in the calorimeter chambers and the chambers are placed in activity monitors. These studies are done during the light cycle. Prior to the measurement of oxygen consumption, the rats are fed standard chow ad libitum. During the measurement of oxygen consumption, food is not available. Basal pre-dose oxygen consumption and ambulatory activity are measured every 10 minutes for 2.5 to 3 hours. At the end of the basal pre-dosing period, the chambers are opened and the animals are administered a single dose of compound (the usual dose range is 0.001 to 10 mg/kg) by oral gavage (or other route of administration as specified, i.e. s.c., i.p., i.v.). Drugs are prepared in methylcellulose, water or other specified vehicle (examples include PEG400, 30% beta-cyclo dextran and propylene glycol). Oxygen consumption and ambulatory activity are measured every 10 minutes for an additional 1-6 hours post-dosing.

The Oxymax calorimeter software calculates the oxygen consumption (ml/kg/h) based on the flow rate of air through the chambers and difference in oxygen content at inlet and output ports. The activity monitors have 15 infrared light beams spaced one inch apart on each axis, ambulatory activity is recorded when two consecutive beams are broken and the results are recorded as counts.

Resting oxygen consumption, during pre- and post-dosing, is calculated by averaging the 10-min O_2 consumption values, excluding periods of high ambulatory activity (ambulatory activity count > 100) and excluding the first 5 values of the pre-dose period and the first value from the post-dose period. Change in oxygen consumption is reported as percent and is calculated by dividing the post-dosing resting oxygen consumption by the pre-dose oxygen consumption *100. Experiments will typically be done with n = 4-6 rats and results reported are mean +/- SEM.

Interpretation:

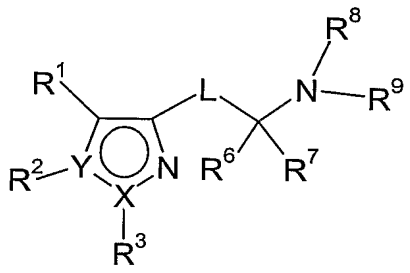
An increase in oxygen consumption of >10% is considered a positive result. Historically, vehicle-treated rats have no change in oxygen consumption from pre-dose basal.

5

CLAIMS

What is claimed is:

1. A compound of Formula (I)



(I)

wherein

X is carbon and Y is nitrogen or X is nitrogen and Y is carbon;

R^1 is hydrogen, $(C_1$-$C_6)$alkyl, halogen, or cyano;

R^2 and R^3 are each independently $(CH_2)_n$-aryl or $(CH_2)_n$-heteroaryl, where n is 0, 1 or 2, and where said aryl and said heteroaryl moieties are optionally substituted with one or more substituents;

L is -C(O)- or $-C(R^4)(OR^5)-$, where R^4 is hydrogen or $(C_1$-$C_6)$alkyl and R^5 is hydrogen, $(C_1$-$C_6)$alkyl, or taken together with R^8 or R^9 is $-CH_2CH_2-$ or $-CH_2C(O)-$;

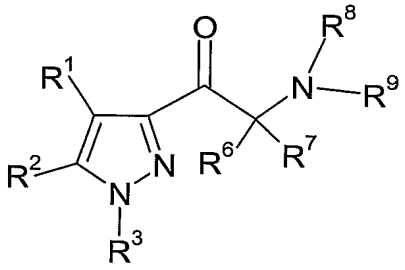
R^6 and R^7 are each independently hydrogen or $(C_1$-$C_6)$alkyl, or R^6 and R^7 taken together form a partially or fully saturated carbocyclic ring; and

R^8 and R^9 are each independently hydrogen, $(C_1$-$C_6)$alkyl, $-C(O)(CH_2)_mR^{10}$, $-SO_2(CH_2)_nR^{10}$, or $-(CH_2)_pR^{10}$, where m and n are 0, 1, or 2, p is 0, 1, 2 or 3, and R^{10} is selected from the group consisting of $(C_1$-$C_8)$alkyl, a partially or fully saturated cycloalkyl, aryl, heteroaryl, and a partially or fully saturated heterocycle, where said $(C_1$-$C_8)$alkyl, said cycloalkyl, said aryl, said heteroaryl and said heterocycle are optionally substituted with one or more substituents; or

R^8 and R^9 taken together form a partially or fully saturated, 4- to 8-membered heterocyclic ring containing 1 to 3 heteroatoms and optionally substituted with one or more substituents;

a pharmaceutically acceptable salt thereof, a prodrug of said compound or said salt, or a solvate or hydrate of said compound, said salt or said prodrug.

2. The compound of Claim 1, wherein said compound of Formula (I) is a compound of Formula (IA)



(IA)

wherein

R^1 is hydrogen or $(C_1\text{-}C_6)$alkyl;

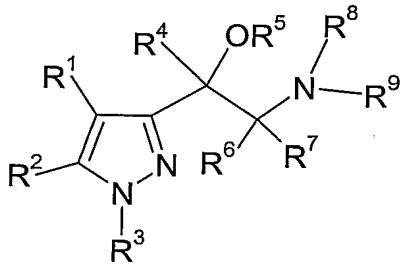
R^2 and R^3 are each independently $-(CH_2)_n$-aryl or $-(CH_2)_n$-heteroaryl, where n is 0, 1 or 2, and where said aryl and said heteroaryl moieties are each optionally substituted with one to three substituents; and

R^6 and R^7 are each independently hydrogen or $(C_1\text{-}C_6)$alkyl, or R^6 and R^7 taken together form a partially or fully saturated carbocyclic ring; and

R^8 and R^9 taken together form a partially or fully saturated, 5- to 7-membered heterocyclic ring containing 1 to 3 heteroatoms and optionally substituted with one or more substituents;

a pharmaceutically acceptable salt thereof, a prodrug of said compound or said salt, or a solvate or hydrate of said compound, said salt or said prodrug.

3. The compound of Claim 1, wherein said compound of Formula (I) is a compound of Formula (IB)



(IB)

wherein

R^1 is hydrogen or $(C_1\text{-}C_6)$alkyl;

R^2 and R^3 are each independently $-(CH_2)_n$-aryl or $-(CH_2)_n$-heteroaryl, where n is 0, 1 or 2, and where said aryl and said heteroaryl moieties are each optionally substituted with one to three substituents;

R^4 is hydrogen or $(C_1\text{-}C_6)$alkyl;

R^5 is hydrogen or $(C_1\text{-}C_6)$alkyl;

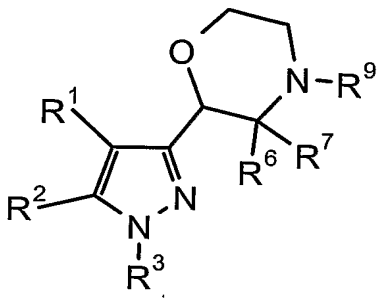
R^6 and R^7 are each independently hydrogen or $(C_1\text{-}C_6)$alkyl, or R^6 and R^7 taken together form a partially or fully saturated carbocyclic ring; and

R^8 and R^9 are each independently hydrogen, $(C_1\text{-}C_6)$alkyl, $-C(O)(CH_2)_mR^{10}$, $-SO_2(CH_2)_nR^{10}$, or $-(CH_2)_pR^{10}$, where m and n are 0, 1, or 2, p is 0, 1, 2 or 3, and R^{10} is selected from the group consisting of $(C_1\text{-}C_8)$alkyl, a partially or fully saturated cycloalkyl, aryl, heteroaryl, and a partially or fully saturated heterocycle, where said $(C_1\text{-}C_8)$alkyl, said cycloalkyl, said aryl, said heteroaryl and said heterocycle are optionally substituted with one or more substituents, or

R^8 and R^9 taken together form a partially or fully saturated, 5- to 7-membered heterocyclic ring containing 1 to 3 heteroatoms and optionally substituted with one or more substituents;

a pharmaceutically acceptable salt thereof, a prodrug of said compound or said salt, or a solvate or hydrate of said compound, said salt or said prodrug.

4. The compound of Claim 1 wherein said compound of Formula (I) is a compound of Formula (IC)



(IC)

wherein

R^1 is hydrogen or $(C_1\text{-}C_6)$alkyl;

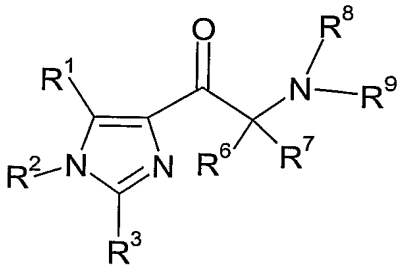
R^2 and R^3 are each independently $-(CH_2)_n$-aryl or $-(CH_2)_n$-heteroaryl, where n is 0, 1 or 2, and where said aryl and said heteroaryl moieties are each optionally substituted with one to three substituents;

R^6 and R^7 are each independently hydrogen or $(C_1\text{-}C_6)$alkyl, or R^6 and R^7 taken together form a partially or fully saturated carbocyclic ring; and

R^9 is hydrogen, $(C_1\text{-}C_6)$alkyl, $-C(O)(CH_2)_mR^{10}$, $-SO_2(CH_2)_nR^{10}$, or $-(CH_2)_pR^{10}$, where m and n are 0, 1, or 2, p is 0, 1, 2 or 3, and R^{10} is selected from the group consisting of $(C_1\text{-}C_8)$alkyl, a partially or fully saturated cycloalkyl, aryl, heteroaryl, and a partially or fully saturated heterocycle, where said $(C_1\text{-}C_8)$alkyl, said cycloalkyl, said aryl, said heteroaryl and said heterocycle are optionally substituted with one or more substituents;

a pharmaceutically acceptable salt thereof, a prodrug of said compound or said salt, or a solvate or hydrate of said compound, said salt or said prodrug.

5. The compound of Claim 1, wherein said compound of Formula (I) is a compound of Formula (ID)



(ID)

wherein

R^1 is hydrogen or $(C_1\text{-}C_6)$alkyl;

R^2 and R^3 are each independently $-(CH_2)_n$-aryl or $-(CH_2)_n$-heteroaryl, where n is 0, 1 or 2, and where said aryl and said heteroaryl moieties are each optionally substituted with one to three substituents;

R^6 and R^7 are each independently hydrogen or $(C_1\text{-}C_6)$alkyl, or R^6 and R^7 taken together form a partially or fully saturated carbocyclic ring; and

R^8 and R^9 taken together form a partially or fully saturated, 5- to 7-membered heterocyclic ring containing 1 to 3 heteroatoms and optionally substituted with one or more substituents;

a pharmaceutically acceptable salt thereof, a prodrug of said compound or said salt, or a solvate or hydrate of said compound, said salt or said prodrug.

6. The compound of any one of the preceding claims wherein R^2 is *p*-chlorophenyl or *p*-fluorophenyl, and R^3 is 2,4-dichlorophenyl, 2-chlorophenyl or 2-flurorophenyl.

7. The compound of Claim 1 selected from the group consisting of

1-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-piperidin-1-yl-ethanone;

1-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-morpholin-4-yl-ethanone;

1-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-(1-methyl-1H-pyrrole-2-carbonyl)-piperazin-1-yl]-ethanone;

1-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-(1-methyl-cyclopropanecarbonyl)-piperazin-1-yl]-ethanone;

N-(1-{2-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-piperidin-4-yl)-2,2,2-trifluoro-acetamide;

1-[5-(4-chloro-phenyl)-1-(2-fluoro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-morpholin-4-yl-ethanone;

1-[5-(4-chloro-phenyl)-1-(2-fluoro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-piperidin-1-yl-ethanone;

1-[5-(4-chloro-phenyl)-1-(2-fluoro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-(4-trifluoroacetyl-piperazin-1-yl)-ethanone;

1-[1-(2-chloro-phenyl)-5-(4-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-pyrrolidin-1-yl-ethanone;

1-[1-(2-chloro-phenyl)-5-(4-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-[1,4]oxazepan-4-yl-ethanone;

1-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-(1-oxa-8-aza-spiro[4.5]dec-8-yl)-ethanone;

2-(benzyl-isopropyl-amino)-1-[1-(2-chloro-phenyl)-5-(4-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-ethanol;

1-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-(3,5-dimethyl-piperidin-1-yl)-ethanol;

1-{2-[1-(2-chloro-phenyl)-5-(4-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-hydroxy-ethyl}-4-isopropylamino-piperidine-4-carboxylic acid amide;

1-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-(3,3-dimethyl-piperidin-1-yl)-ethanol;

1-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-piperidin-1-yl-ethanol;

1-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-morpholin-4-yl-ethanol;

2-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-4-cyclohexyl-morpholine;

2-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-4-(propane-2-sulfonyl)-morpholine;

2-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-4-(toluene-4-sulfonyl)-morpholine;

1-{2-[1-(2-chloro-phenyl)-5-(4-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-morpholin-4-yl}-2-methyl-propan-1-one;

2-[1-(2-chloro-phenyl)-5-(4-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-4-(4-trifluoromethyl-benzyl)-morpholine;

1-[1-(4-chloro-phenyl)-2-(2,4-dichloro-phenyl)-5-methyl-1H-imidazol-4-yl]-2-piperidin-1-yl-ethanone; and

1-[1-(4-chloro-phenyl)-2-(2,4-dichloro-phenyl)-5-methyl-1H-imidazol-4-yl]-2-morpholin-4-yl-ethanone;

a pharmaceutically acceptable salt thereof or a solvate or hydrate of said compound or said salt.

8. A pharmaceutical composition comprising

(a) a compound of any one of the preceding claims, a pharmaceutically acceptable salt thereof, a prodrug of said compound or said salt, or a solvate or hydrate of said compound, said salt or said prodrug; and

(b) a pharmaceutically acceptable excipient, diluent, or carrier.

9. The composition of Claim 8 further comprising a nicotine partial agonist, an opioid antagonist, a dopaminergic agent, or an anti-obesity agent.

10. A method for treating a disease, condition or disorder modulated by a cannabinoid receptor antagonist in animals comprising the step of administering to an animal in need of such treatment a

therapeutically effective amount of a compound of Claim 1, 2, 3, 4, 5, 6, or 7, a pharmaceutically acceptable salt thereof, a prodrug of said compound or said salt, or a solvate or hydrate of said compound, said salt or said prodrug.

11. The method of Claim 10 wherein said disease, condition or disorder modulated by a cannabinoid receptor antagonist is obesity, alcoholism, or tobacco abuse.

12. The use of a compound of Claim 1, 2, 3, 4, 5, 6, or 7, a pharmaceutically acceptable salt thereof, a prodrug of said compound or said salt, or a solvate or hydrate of said compound, said salt or said prodrug, in the manufacture of a medicament for treating a disease, condition or disorder which is modulated by a cannabinoid receptor antagonist

INTERNATIONAL SEARCH REPORT

PCT/IB 03/05835

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D231/12 C07D401/06 C07D401/12 C07D403/06 C07D403/12
C07D417/06 C07D405/12 C07D471/04 C07D413/06 C07D233/64
A61K31/4155 A61K31/415 A61K31/4427 A61K31/4709 A61K31/4725

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, PAJ, CHEM ABS Data, EPO-Internal, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	WO 03 027076 A (HERREMANS ARNOLDUS H J ;KRUSE CORNELIS G (NL); LANGE JOSEPHUS H M) 3 April 2003 (2003-04-03) se whole document	1-12
A	WO 96 14302 A (KOBAYASHI SEIICHI ;ABE SHINYA (JP); EISAI CO LTD (JP); HORIZOE TAT) 17 May 1996 (1996-05-17) see definitions of Y, page 4	1-12
Y	US 5 624 941 A (ANNE-ARCHARD GILLES ET AL) 29 April 1997 (1997-04-29) see definitions of X and R	1-12

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 March 2004	15/03/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Scruton-Evans, I

INTERNATIONAL SEARCH REPORT

PCT/IB 03/05835

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/4178 A61K31/5355 A61K31/506 //(C07D471/04,221:00, 209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	THOMAS B F ET AL: "COMPARATIVE RECEPTOR BINDING ANALYSES OF CANNABINOID AGONISTS AND ANTAGONISTS" JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, AMERICAN SOCIETY FOR PHARMACOLOGY AND, US, vol. 285, no. 1, 1998, pages 285-292, XP000942485 ISSN: 0022-3565 the whole document --- -/--	1-12

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 March 2004	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Scruton-Evans, I

INTERNATIONAL SEARCH REPORT

PCT/IB 03/05835

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	PERTWEE R G: "PHARMACOLOGY OF CANNABINOID RECEPTOR LIGANDS" CURRENT MEDICINAL CHEMISTRY, BENTHAM SCIENCE PUBLISHERS BV, BE, vol. 6, no. 8, 1999, pages 635-664, XP009024021 ISSN: 0929-8673 the whole document	1-12

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-5,8-12(partly)

Present claims 1-5,8-12 relate to a compound defined by reference to a desirable characteristic or property, namely that it be a prodrug of the formula I compounds.
The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds of formula I and their use, and not their prodrugs.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

PCT/IB 03/05835

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 10,11 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-5,8-12(partly)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/IB 03/05835

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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